UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IMMUNEX CORPORATION; AMGEN MANUFACTURING, LIMITED; and HOFFMAN-LaROCHE INC.,

Plaintiffs,

v.

SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; SANDOZ GMBH,

Defendants.

CIVIL NUMBER:
2:16-cv-01118-CCC-JBC

TRIAL
(PM SESSION)

Martin Luther King Building & U.S. Courthouse
50 Walnut Street, Newark, New Jersey 07101
Tuesday, September 11, 2018
Commencing at 1:44 p.m.

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI
UNITED STATES DISTRICT JUDGE

Certified as True and Correct as required by Title 28, U.S.C. Section 753

/S/ Jacqueline Kashmer, CCR, CMR, CRCR

Jacqueline Kashmer, Official Court Reporter
(908) 200-1040
jkcsr711@aol.com

A P P E A R A N C E S:

WALSH PIZZI O'REILLY FALANGA LLP
BY: LIZA M. WALSH, ESQUIRE
MARC D. HAEFNER, ESQUIRE
- and -
SIDLEY AUSTIN LLP
BY: VERNON M. WINTERS, ESQUIRE
DAVID T. PRITIKIN, ESQUIRE
JAMES A. HIGH, JR., ESQUIRE
STEVEN J. HOROWITZ, ESQUIRE
For the Plaintiffs Immunex Corporation and Amgen Manufacturing Limited

GIBBONS, PC
BY: CHARLES H. CHEVALIER, ESQUIRE
- and -
WILLIAMS & CONNOLLY, LLP
BY: AARON MAURER, ESQUIRE
For the Plaintiff Hoffman-LaRoche, Inc.

HILL WALLACK LLP
BY: ERIC I. ABRAHAM, ESQUIRE
CHRISTY L. SAVERIANO, ESQUIRE
-and-
WINSTON & STRAWN LLP
BY: MAUREEN L. RURKA, ESQUIRE
GEORGE C. LOMBARDI, ESQUIRE
JULIA MANO JOHNSON, ESQUIRE
LOREN G. RENE, ESQUIRE
MERRITT D. WESTCOTT, ESQUIRE
For the Defendant Sandoz

ALSO IN ATTENDANCE:

J. DREW DIAMOND, ESQUIRE, Corporate Counsel, Amgen Manufacturing, Limited
STUART WATT, Plaintiffs' Corporate Representative
DAVID WILDMAN, ESQUIRE, Corporate Counsel, Hoffman-LaRoche, Inc.

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(PROCEEDINGS held in open court before The Honorable CLAIRE C. CECCHI, United States District Judge, at 1:44 p.m.)

THE COURT: Are we ready to proceed with the witness?

MR. LOMBARDI: We are, your Honor, and we did confer, so if I may take a moment.

THE COURT: Certainly. Go ahead.

MR. LOMBARDI: We'll be putting Dr. Blobel on direct this afternoon. I expect that that will take most of the afternoon or close to it --

THE COURT: Right.

MR. LOMBARDI: -- which means that he will be on cross as we start the day tomorrow.

THE COURT: Okay.

MR. LOMBARDI: Dr. McCamish is the witness who we need to fit in. He will be a much shorter witness time-wise, less than an hour on direct. And I just -- I talked to Mr. Pritikin, I'm not asking him to make predictions on the cross, but the odds are he will be done with his cross by, say, early afternoon tomorrow.

If we get to three or so tomorrow, I may have to ask your Honor for leave to get Dr. McCamish on, in order to get him off.

THE COURT: I think that's fine. I don't see any issue in that. Do you see any problem in working that out?

MR. PRITIKIN: I agree, your Honor. I really don't. I think we're going to be able to work these things out, your Honor.

THE COURT: Perfect. Okay. So we should just start, and obviously if we come to 3:00 and have to make some sort of arrangement, that's fine.

MR. LOMBARDI: I just wanted to alert you to that.

THE COURT: Very well. Sounds good. Thank you.

MR. PRITIKIN: One other housekeeping matter, your Honor. My team tells me that I misspoke once during the opening.

THE COURT: Okay.

MR. PRITIKIN: I referred to the '279 patent and I said at one point that the claims covered the p75 receptor. If I did say that, and I sure don't remember it, I obviously misspoke. It's the p55.

THE COURT: P55 got it. Thank you so much. Okay.

Mr. Haefner.

MR. HAEFNER: Hello, your Honor. It's our understanding that pursuant to your Honor's request, the parties, prior to the witness, are supposed to lodge any objections that they have that couldn't have been worked out at the meet-and-confer.

THE COURT: Do we have an objection at this point?

MR. HAEFNER: Not to the witness, to the set of

documents. We'd just like to preserve the objections for the record, your Honor.

One, your Honor, is DTX-1164. That's the Beutler declaration that was the subject of the motion in limine. And in our opinion, all the reasons the motion in limine continue to apply, however, your Honor is going to hear about it, to a complete inclusion and defer that decision to the end of the trial.

THE COURT: Okay.

MR. HAEFNER: So we just wanted to note the objection.

THE COURT: Otherwise, that was the subject of the in limine motion which we have ruled upon. And at this point you're just, I guess, voicing your continued position as to was there anything new on that?

MR. HAEFNER: Just an abundance of caution, your Honor.

THE COURT: All right. So there's nothing, then, for the Court to do at this point. You're just noting it again.

MR. HAEFNER: Not that one. And then for DTX-70 and 84, we just wanted to note, again, we think it's objectionable. It's difficult to tell, your Honor, until it comes in in the course of Dr. Blobel's testimony.

THE COURT: Okay.

MR. HAEFNER: These two documents are allegedly background references but they are not on the list of background references and, so, we were told last night that they are have some other purpose and we'd like to see that borne out, of course, and we just wanted to note again for the record, so we can see how it plays out.

THE COURT: You didn't have an opportunity to talk about 70 or 84, or did you?

MR. HAEFNER: We did talk about it last night, your Honor, during the meet-and-confer and the parties weren't able to come to a resolution. It's difficult without the witness testifying.

THE COURT: Okay. So you're suggesting we see how it goes and then you'll be better able to revisit the issue, I guess.

MR. HAEFNER: Yes, your Honor.

THE COURT: And I'm going to say this before we start with the witnesses in terms of objections and so on, because we're dealing with objections to exhibits, but to the extent we're dealing with objections to the questioning, the matter of questioning or the responses, obviously, it's a bench trial, so, I think some of the issues will be a little bit more streamlined than they would be otherwise before a jury and I think we all probably understand that as well, because, ultimately, I

will be reviewing the evidence here as it goes in and to the extent something is not appropriate, I'm going to deem it so at the appropriate time. All right.

MR. HAEFNER: Thank you, your Honor.

THE COURT: Thank you so much. With that, should we start?

MS. RURKA: Yes, your Honor.

We call Dr. Carl Blobel to the stand.

THE COURT: Very well. Thank you.

We'll have the witness sworn in. Good afternoon.

THE WITNESS: Good afternoon.

MS. RURKA: I believe you have all the --

THE COURT: I have piles of stuff before me.

CARL P. BLOBEL, M.D., Ph.D., DEFENSE WITNESS,

having been duly sworn, testifies as follows:

DIRECT EXAMINATION

THE COURT: Thank you.

BY MS. RURKA:

Q. Good afternoon, Dr. Blobel.

A. Good afternoon.

Q. What is your current occupation?

A. I'm senior scientist at the Hospital For Special Surgery, which is an orthopedic hospital in New York City. I'm director of the arthritis and tissue regeneration program, and I'm a professor of medicine and physiology and

and biophysics at Weill Cornell Medicine. It's a medical school in New York City.

Q. Dr. Blobel, do you conduct scientific research?

A. Yes, I do.

Q. Okay. What kind of scientific research?

A. My lab is interested in studying biomedical -- we're involved in biomedical research. In particular, we're studying the role of a molecule called the TNF convertase in development and disease -- in diseases such as rheumatoid arthritis.

But I would -- the medical school and my work involves basic research, research in models for disease and also involves with human patients, if possible.

Q. How long have you been involved in this field?

A. Over 30 years. About 34 years.

Q. Okay. So let's talk briefly about your background and your expertise.

Did you bring your CV to the court?

A. Yes, I did.

Q. Okay. Can you turn to DTX-1246.

Is this your current CV?

A. Yes, this is my curriculum vitae.

Q. And can you just briefly describe your educational background and when you received your degrees?

A. Yes, I can. I received my M.D. degree in 1984, from

the Justus-Liebig University in Giessen, Germany.

I then obtained the Educational Commission for Pharma Medical Graduate certificate; that's at the equivalent of a U.S. M.D.

I also had an additional degree from Germany called the Dr. Med., and began graduate school at UCSF, University of California in San Francisco, in 1985, and graduated in 1991, with a Ph.D. biochemistry and biophysics.

Q. Can you describe your graduate research?

A. Yes, I can. My graduate research was focused on identifying a membrane fusion protein or a sperm egg fusion protein. And we used many of the same techniques, or I, in fact, used many of the same techniques that will be discussed here, which ranged from cDNA cloning, production of fusion protein, cell biology, cell culture, and so forth.

Q. After receiving your Ph.D. what did you do?

A. I was a post-doctoral fellow -- that's the next step in such a career -- for one year, at UCSF, still in California. And then was fortunate to be recruited, actually to several universities, and ended up going to the Memorial Sloan Kettering Cancer Center to start my own lab.

I stayed there for about 12 years and then moved across the street, to the Hospital For Special Surgery, where I have been since 2004.

Q. And can you provide some relevant examples of the research you've completed after your post-doctoral fellowship?

A. Yes, I can. We are working on molecular scissors that are on the cell's surface and will activate cytokines such as TNF-a, which we will speak about much more later. And from that point of view, I'm very familiar, actually, with TNF-a, with its receptors, with the functions of TNF-a in autoimmune diseases.

We have published on, for instance, models for rheumatoid arthritis, for lupus, for hemophiliac arthropathy.

So our work really is meant to range -- or ranges, also due to my education as a Ph.D. in biochemistry and biophysics and M.D., sort of spans the gamut working with molecules, with cells, and with patients.

Q. How many articles have you published in your career, Doctor?

A. About 127, 128 at this point.

Q. And have you received recognition from your peers relating to your research?

A. Yes, I have. And there are, perhaps, two to highlight on this list.

One was the award of Hans Fischer Senior Fellowship from the Institute of Advanced Studies at the Technical

University in Munich. That's one of the top universities in Munich. And that was to initiate collaborations in Munich, for instance, on Alzheimer's disease.

The other honor is the election to the Association of American Physicians. This is an association of physician scientists in the U.S.

Sixty physician scientists are elected every year based on their lifetime contribution in biomedical research and, so, that was certainly a great honor to me to be elected into that society.

Q. And can you -- have you served on editorial or scientific advisory boards in your field?

A. Yes, I have. On quite a few, actually. But just like to highlight a few examples for today, and those are on the next slide.

So, for instance, I took part in what's called an NIH Study Section. That was for a full term of four years, where we review grants and research applications from other scientists.

I have also served on the editorial board of several scientific journals and would like to highlight here, for example, the *Journal of Biological Chemistry and the journal called Cancer Research*.

MS. RURKA: So, your Honor, we'd like to offer Dr. Blobel as an expert in the field of biochemistry,

molecular biology, recombinant DNA technology, and molecular immunology.

THE COURT: Any objection?

MR. PRITIKIN: No objection.

THE COURT: He is admitted for those purposes. Thank you.

MS. RURKA: Thank you, your Honor.

BY MS. RURKA:

Q. So have you prepared some slides to assist in your testimony today?

A. Yes, I have.

Q. Let's go to DDX-1001.

And this is kind of a road map of your opinions in this case. Is that right, Doctor?

A. Yes. It's an outline, yeah, of what I plan to discuss today.

Q. Can you just go through what you're planning to discuss today with the outline in mind?

A. Yes. We will start with the brief technical background, which is important to understand what TNF is and what etanercept is; a background in molecular cell biology.

We will then -- I will then discuss TNF and etanercept, what that is and what it is made up of.

Following that, I will discuss obviousness-type

double patenting in the context of the '182 and the '522 patents that are at case here, and I will support my opinion that these patents are invalid for reasons of obviousness-type double patenting over other patents, the Finck patents on psoriasis and the Jacobs patents.

I will then, on top of that, discuss obviousness; why, at the cutoff date of August 1990, it would have been obvious to generate a molecule like etanercept.

And then there will be brief discussions of anticipation and obviousness at a later date.

And finally, we will end, very briefly, on an obviousness-type double patenting discussion of the Brockhaus '279 patents.

Q. Okay. So before we do that, let's talk about the patents-in-suit briefly.

If you could turn to JTX-1 in your binder.

A. So this is the first patent.

Q. Yes. Can you identify it?

A. It's the '182 Brockhaus patent filed by Manfred Brockhaus, and the title of it is, "Human TNF Receptor Fusion Protein."

Q. And you understand you're offering opinions on the asserted claims, which are 11, 12, 35 and 36. Is that right Doctor?

A. That's correct.

Q. And what are those generally directed to?
A. Those claims are generally directed to a fusion protein between the p75 TNF receptor and the hinge-CH2-CH3 region of an IgG1 molecule, which is essentially etanercept. So that's what they're directed to.
Q. And can you turn to -- is that JTX-2 in your binder?
A. Yes.
Q. And what is this patent?
A. This is the second Brockhaus patent. It's the '522 patent. It is, in terms of the molecule, very similar, essentially identical.
The main difference between the '182 and the '522 patents is that this '522 patent describes a method to produce etanercept.
Q. Okay. And you understand you're offering an opinion on asserted claims 3, 8 and 10. Is that right?
A. That's correct.
Q. Okay. So, why don't we start with an explanation of etanercept, since that's what the patents -- the asserted claims are directed to.
MS. RURKA: And can we turn to DDX-1002.
BY MS. RURKA:
Q. And can you just kind of walk through what etanercept is and the parts that it's made of?
A. Yes, I can, of course.

This is a demonstrative I prepared to illustrate etanercept in the middle. And I will go into much more detail on this, but for the purpose of introductory slide, I have highlighted the extracellular domain of the p75 receptor in green here, which is sitting on a membrane.

And I have shown, on the right-hand side an immunoglobulin. Again, we'll speak about more that. And highlighted the hinge CH2 and CH3 portion of the immunoglobulin in the blue box.

And as you can see, etanercept is a combination of chimeric protein and fusion protein consisting of the extracellular portion -- consisting of the extracellular domain of the p75 TNF receptor linked to the hinge CH2 and CH3 domain of the human IgG. So this is what etanercept looks like.

Q. Okay. And so, since etanercept is a protein, why don't we start with just a general discussion of protein and protein expression.

MS. RURKA: And if we can go to DDX-1004.

BY MS. RURKA:

Q. And we're now in kind of the technical background here part of your testimony, just for purposes of road mapping.

Why don't we -- can you give us a general idea of what a protein is and what it's made up of?

A. Yes. So I prepared several demonstratives to illustrate that point, actually.

What we see here is a very simple model of a protein, which you can imagine is essentially beads on a string, from dozens to several hundred beads on a string.

Proteins are the molecules that support life, so, they can fold in different ways, which I'll get into on the next few slides. But this is sort of a general concept. It's beads on a string, and they can support life. They can do things.

Q. What are the beads made -- what are the beads?

A. The individual beads are called amino acid residues. And I prepared a demonstrative to illustrate that as well.

Q. Okay. We're on DDX-1005.

And what are you describing here, Doctor?

A. This demonstrative shows, on the left-hand side, a list of the -- in some cases rather cumbersome names of the different amino acids. I'll read a few.

Isoleucine, leucine, valine, phenylalanine. Because scientists, when they describe the order of beads, do not want to write these out, they have agreed on two very simple codes. One is the single-letter code and, so, an isoleucine turns into an "I", and a leucine turns into an "L", or there can be a three-letter code where an isoleucine turns into "ILE" and leucine into an "LEU".

Really the main reason I'm bringing this up is that every one of these building blocks has somewhat different properties and different shapes, in a sense and, so, it really matters in what order you string them up, the individual beads on a string, because depending on the order, it will impart certain structures and functions onto the protein, which I've illustrated on the next demonstrative.

Q. Okay. So, let's turn to DDX-1006, and can you describe the folding of proteins and how they affect structure and function?

A. Yes, I can. On the left-hand side I placed the same protein that we were just looking at. And through a series of events, it can fold into a folded protein.

And the beauty of this really in the body is that each of these folded proteins is folded so precisely that you can imagine it being like a key in a lock and, so, only a certain key will fit into a certain lock; or for what we will be getting to later, a certain cytokine, such as TNF-a, can only bind to certain receptors because they're folded just so.

Q. Okay. And how are proteins created, Doctor?

A. Can we turn to the next demonstrative?

Q. Absolutely. DDX-1007.

A. Each of our cells contains a nucleus that essentially

contains the information or the DNA that I think we're all familiar with, our -- it's in our DNA. And the DNA is basically a series of letters, about 3.2 billion of them, and they encode about 20,000 or so proteins, we think right now.

And so, for the DNA in the nucleus to instruct the cell to make these proteins, what happens is if you imagine the DNA to be a booklet, say, with 20,000 pages, the cell can go ahead and transcribe an individual page to make a protein, send that information outside, and then it is translated through a fascinating machinery into your protein, which ultimately proceeds to fold and turn into the specific structure that I just described earlier.

Q. Okay. So, can you just generally describe the relationship between the DNA sequence and the amino acid sequence then?

A. The DNA sequence is said to encode the amino acid sequence. So, there are so-called genes or it can be a fusion protein that one would make, and you can thereby, by putting the DNA sequence together in a certain way, task the cell to make a protein at will. And that will contain any of the building blocks as you will put them together.

Q. Okay. And how many DNA codons do you have for a single amino acid?

A. So, for every single amino acid this is the genetic

code, several level prizes were actually given for this information, you have three letters of DNA information for one amino acid residue.

Q. Okay. And were there methods available to a person of skill in the art in 1990 to create these proteins?

A. Absolutely. This was actually also the time that I was in graduate school, and the so-called molecular biology revolution had occurred a few years beforehand.

What was exciting about that is there were actually ways to manipulate genes and to make -- to get cells to make certain proteins. I prepared a demonstrative for that as well.

Q. Let's go to DDX-1008, and why don't you walk us through briefly what this -- what the methods were.

A. Yes. So, what was really the main breakthrough at the time is that scientists understood that you could not only look at pieces of DNA that were in the nucleus, but you could isolate individual fragments.

Let's say you could tear a page out of the book that contained one DNA or gene of interest, and then you could place that into a plasmid loop, basically a small piece of DNA that you could shuttle back and forth and make many, many copies of, and introduce it into a cell, which is shown here on the right-hand side.

So, you could place your DNA of interest, which will

tell the cell to make a certain protein, into the cell. It then enters the nucleus and instructs the cell to make the protein that you are telling it to make; of course, among many other molecules that it's making on its own.

Q. Okay. And then let's go to DDX-1009, and then what happens next? How do you grow the host cells and make the proteins?

A. The demonstrative I prepared here is, in a sense, meant to illustrate, actually, a scaling up of this type of a production that you would have to do to make a drug such as etanercept.

So, you'd have here your host cell. And you put it into a huge fermenter where you can grow large amounts of these cells, and they're sitting in a broth and they will secrete the cell into the medium, so, you see these little wheel-shaped structures would be your protein of interest.

Now, as I said, they will be sitting in a medium together with many other molecules. And an important part of isolating a drug is the ability to purify it into homogeneity basically. And once you're able to do that, you can put it into a formulation and turn it into a medicine.

Again, so etanercept would be an example, but there are many others.

Q. Okay. And, again, would -- were these methods known

in the art in August of 1990?

A. Every one of them was not only known in the art, but very standard. And as a graduate student, we used everything except for the high-scale production.

Q. Okay. So, let's turn to DDX-1010, and let's talk about the next part of your opinion, which is to discuss TNF and etanercept.

First of all, what is -- why don't we start with TNF. What is TNF, Doctor?

A. I prepared a demonstrative here for this. This is a quote actually by Mark Feldman, who is one of the discoverers of TNF. It's the fire alarm of the body. TNF stands for tumor necrosis factor, and it was recognized that it has this function in the body where it can help protect from invaders.

So, if some bacteria come in through the skin, for example, there are professional immune cells that will detect this and they will activate the production of TNF. And that helps you have sort of a localized focal inflammation.

However, unfortunately, in diseases such as rheumatoid arthritis and autoimmune diseases, there is, for reasons that we don't understand very well, too much TNF, and that's called a disregulated activity and, so, that can cause disease when overactive, essentially.

So, there's sort of a yin yang, good and bad side of the TNF. And today we're mainly concerned with the disregulated activity because that's what one would intend to block.

Q. Okay. And if you turn to DDX-1012 , can you describe what causes the biological effect generally for TNF, what -- how does TNF cause its biological influence?

A. Yeah. So, here I prepared a demonstrative that now includes a diagram of a cell that has a boundary. There are receptors here. This is TNF, which will bind to a receptor.

The cell has a boundary, and you have to be able to transmit a signal from the outside to the inside. That's precisely what this receptor does. And when it sees a molecule of TNF, it can elicit a normal activity, which is indicated by this bold-like structure here.

Q. And if we turn to DDX-1013, what happens when TNF is disregulated or there's too much TNF in the body?

A. So, in this case I modified the diagram in a sense to actually show too many molecules of TNF, and there would be more floating around. And now, instead of having one receptor occupied, you have all three occupied.

So, you have three, in a sense, more of these lightning bolts, you have too much activity, you have disregulated inflammation. And when this happens in the

body, it can lead to the swelling and inflammation of joints, painful condition, that you would try to block, in fact, by blocking TNF off.

Q. And was this information known to a person of skill in the art as of August 1990?

A. Yes. As we will discuss in much more detail today, TNF was really a focus of many studies. It was a hot molecule. It was clear it had detrimental effects, so, yes.

Q. Okay. So, let's talk about the receptor itself. And if we go to DDX-1014, can you talk through the parts of the TNF receptor?

A. Yes, of course. I have put together a demonstrative here that shows the different parts of the p75 TNF receptor I briefly alluded to.

First of all, there's an extracellular region that's sitting outside of the cell. This would be the cell boundary.

And for the purpose of today, the main point is that this part, this is the business end that binds TNF. Then when TNF comes in, the inside and outside of the cell are very carefully protected from one another. There's this boundary called the membrane.

And so a receptor has to reach across this boundary and talk to the inside of the cell. That's called the

intracellular region.

And so, here I just like to distinguish between extracellular region, the transmembrane region, and the intracellular region; the extracellular part being the business end that binds TNF that we're interested in.

Q. And as of August 1990, how many TNF receptors were absolutely known to exist?

A. At that point, it was clear there was at least two receptors that existed.

Q. Okay. Let's go to DDX-1015, and can you talk through the two receptors that were known to have existed in August of 1990?

A. Yes. I've put them on this demonstrative, essentially, in different colors. And the other difference is, as you can see, here is the p75 that we just talked about, here's a p55. And that gives me an opportunity to introduce this nomenclature of the p55.

So that's a way for scientists to indicate the size of the molecular weight of a molecule. This stands for protein of 55 kilodalton. The details really don't matter, but the larger the number, the larger the molecule. And so, the p55 TNF receptor, again, has about 55 kilodalton; and the p75, about 75. And that's a handy way to tell them apart.

Q. Okay. And it -- the patents-in-suit, the asserted

claims refer to a measurement of kD. What does that stand for?

A. That stands for kilodalton or a thousand dalton. So, this -- the p55 would be about 55,000 dalton. Again, that's cumbersome, so we say kD instead.

Q. Okay. So, let's go to DDX-1016, and is there a way to separate out the extracellular part of the TNF receptor?

A. There is. And at the time it was actually clear from studies that I'll also say more about, that the cells would actually naturally cut off the extracellular part of the receptor shown here.

And just as an aside, the scissors that do this are the main focus of our work. But at the time it was known that there are soluble forms of these receptors that combine TNF.

Q. And what was known about the potential uses for these receptors in August of 1990?

A. The soluble receptors had, again, in their own right, generated a substantial amount of interest simply because they could block the functions of TNF and, as I said earlier, that was a goal of many scientists.

And the general concept was if you have a soluble receptor, it can scavenge TNF, and it can scavenge and bind it before it actually binds to the cell. So, these are called competitive inhibitors, but just basically they

would prevent the signal. They're inhibitors of TNF.

Q. Okay. So, let's go back to DDX-1002. We have talked about the p75 TNF receptor. That's the top part of etanercept.

Let's talk a little bit about the bottom part of etanercept, which is this portion of an IgG1 immunoglobulin.

And if we go to DDX-1018, can you talk through what an immunoglobulin is generally?

A. Yes. So, I believe that most people will be familiar with this general outline, this sort of Y-shaped depiction of an antibody. An antibody does what the name says, it's against -- it's a body that will detect antigens.

So, antigens can be on the surface of a bacteria or a virus, for example. And the cell or the body uses antibodies to detect these invaders that it's seen before and attack them. So, that's one of the main functions that antibodies have.

Q. Okay. And if we go to DDX-1019, can you just walk us through kind of the different types of structures in an IgG1?

A. Yes, I can. I prepared a number of demonstratives to address this. This is the first one. Antibodies were, of course, also of great interest. And scientists tend to try to describe different parts of what they study.

Here was one way of looking at antibodies in that they have a light chain and a heavy chain. Again, it's very simple to see the light chains are shorter than the heavy chains. And the antibodies also consist of essentially two heavy chains and two light chains, such that one light chain is linked to a heavy chain, and then you have the mirror image on the other side.

Q. Okay. And let's talk about the domains of an immunoglobulin.

MS. RURKA: If we could go to DDX-1020.

BY MS. RURKA:

Q. And can you describe what the domains are of a human IgG1 immunoglobulin?

A. Yes. So, this is another sort of more functional way of looking at an immunoglobulin. And that is to divide it into what's called a variable region, that is the front part that binds to an antigen; and the constant region, which is the business end of an antibody molecule, for instance, holds it together as a dimer. So, this is basically another way of looking at it.

And then to further define terms that will also emerge later in the testimony, the nomenclature included a description of the variable light chains, so that's the "VL" shown here; and the variable heavy chain. And then there was also a constant region of the light chain, and a

constant region 1, 2, and 3 of the heavy chain, as well as a hinge domain.

So, these are operational ways for scientists to describe what they're working on in different parts of an antibody.

Q. Okay. So just to sum up, "C" stands for constant, "V" stands for variable, "L" stands for light, "H" stands for heavy. Is that right?

A. That's exactly right.

Q. Okay. Let's talk about the Fc portion of an immunoglobulin molecule because we'll be seeing a lot of that. And can you describe how scientists talk about the Fc portion?

A. The Fc portion is the so-called crystallizable portion, and it's the portion that's outlined here in this yellow box that consists of the hinge-CH2 and CH3 domain.

Q. So, let's go back to DDX-1002, and where in etanercept does the extracellular region of the p75 TNF receptor attach to an IgG1 immunoglobulin?

A. So, what I'm showing here, again, is the same demonstrative, the same one that we had at the outset -- that I had at the outset. And that's the extracellular domain of the p75 linked to precisely the hinge-CH2 and CH3 portion of a human IgG, and that's etanercept.

Q. Okay. And can we go to DDX-1022, and when you put

these pieces together, can you explain how etanercept works to specifically bind TNF?

A. Yes. So, this is the same concept actually as the soluble receptors that work as inhibitors of TNF. They can scavenge or sequester TNF, act as decoys and bind -- they can scavenge TNF or act as a decoy, and thereby prevent it from binding to the receptors on the cell, and thereby prevent the detrimental functions of TNF.

Q. Okay. Thank you, Doctor.

Why don't we move to your opinions in this case that are related to patent validity, and let's start with a general overview of the perspective that you applied in doing your analysis here.

Did you do -- did you apply a certain perspective when you did your analysis of obviousness-type double patenting and obviousness?

A. Yes, I did.

Q. What perspective did you apply?

A. It was the perspective of a person of ordinary skills in the art.

Q. And did you use a particular date?

A. Yes, of course. It would have -- it was prior to August 1990.

Q. Okay. So, let's turn to DDX-1024, and this contains the definition that you set forth. Can you just describe

what the -- what a person of ordinary skill in the art would have been, in your opinion, as of August 31st, 1990?

A. In my opinion, it would have been a scientist with an advanced degree, could be an M.D. or a Ph.D. degree, in biology, molecular biology, biochemistry, chemistry or a similar field. MDs can also acquire knowledge in those areas.

I would expect this person to have one to two years of experience in the field of immunology or molecular immunology, including experience with cloning and expression of DNA, protein biochemistry on cell culture, protein purification and immunological assays.

And as I also mentioned earlier, while I was a graduate student at UCSF from 1985 to 1991, I actually performed all of these different Techniques and, therefore, was viewing this as a -- as I -- you know, I was a person of ordinary skill in the art and was also viewing it from that perspective.

Q. And that's because you had an M.D. at that point. Is that right, Doctor?

A. I had an M.D. at that point, and was in training for my Ph.D.

Q. Okay. And you understand Dr. Wall has a -- Plaintiff's expert, Dr. Wall, has a definition of person of ordinary skill in the art. You've seen that. Right?

A. I've seen that.
Q. Does it differ in any material respect with your definition?
A. It does not. And if I apply Dr. Wall's criteria, my opinion would not change.
Q. Okay. And you would also still be a person of ordinary skill in the art. Is that right?
A. Just the same.
Q. Okay. Let's turn to DDX-1025, and talk about double patenting. So, you understand you used two different -- you looked at two different patent -- sets of patent claims. Right, Doctor?
A. That's correct.
Q. And which two claim -- which two sets of claims did you look at?
A. One set of claims is summarized on this demonstrative as the psoriasis patents, that's Finck '225, '605 and '631. And the other patent is the Jacobs patent, that's the '690 patent.
Q. Okay. And so, can you just generally explain -- why don't we start with the psoriasis patents. Can you generally explain what the claims of the psoriasis patents are or what they're directed to?
A. The psoriasis patents are directed to using etanercept to treat psoriatic conditions.

Q. Okay. And you provided an expert report in this case. Isn't that right, Doctor?
A. That's correct.
Q. And it included an analysis of the psoriasis patents in the claims. Right?
A. Yes.
Q. What evidence, apart from your opinion and the documents you relied on, have you seen related to the non-obviousness of the patents-in-suit, the claims of the patents-in-suit, as compared to the psoriasis patent claims?
A. I have not seen other evidence offered by plaintiffs' experts.
Q. Okay. So let's go through just the analysis here to get it into the record.
Can you turn to JTX-39.
A. Yes.
Q. Yes? Okay. And what is this, Doctor?
A. This is the first of the three Finck patents. It's the '225 patent by the inventor Barbara Finck, and it's by the Immunex Corporation.
Q. And what is it generally directed to?
A. It's directed to the use of etanercept to treat the psoriatic condition.
Q. Okay. And if you can turn to JTX-40. And what is

this patent, Doctor?

A. This is the second Finck patent, the '605 Finck patent, again, the same inventor and it is also the Immunex Corporation.

Q. And what is this patent directed to?

A. It's for the use of etanercept to treat the psoriatic condition.

Q. Okay.

MS. RURKA: And then if we turn to JTX-41.

BY MS. RURKA:

Q. What is this patent, Doctor?

A. This is the third of the series of Finck patents. It's the '631 patent, also filed by Barbara Finck at the Immunex Corporation, and it also covers the treatment of the psoriatic condition with etanercept.

Q. Okay. Let's turn to Page 17 of JTX-41. This is still the '631 patent, and let's take a look at Claim 1. And if you could just walk us through what this claim is directed to.

A. Yes. So let me explain what this means. It's a method of treatment comprising administering a dose of TNFR, TNF receptor Fc, to a patient having psoriatic arthritis and/or plaque psoriasis.

So this claim refers to a TNF receptor Fc, and it refers to the administration of the TNF receptor Fc as a

drug to a patient.

Q. Okay. And the three "wherein" elements, what are those generally directed to?

A. So those are elements directed to treatment and administration.

Q. Okay.

MS. RURKA: Let's pull up DTX- -- or DDX -- I'm sorry -- 1021 -- 1027. Sorry.

BY MS. RURKA:

Q. We did a -- you prepared a chart here of the different Finck patent claims. Is that right?

A. Yes. Because it makes it easier for me to draw a comparison between the claims and also to show their similarity.

The main point of this chart is that each of them claims a TNF receptor Fc, shown here in green and blue in the color code that we're using throughout to denote the different fragments of etanercept. And then it discusses what it should be used for, and here are the three psoriatic conditions, so psoriasis -- ordinary psoriasis, plaque psoriasis or psoriatic arthritis.

Q. Okay. And how do you know TNFR:Fc is etanercept?

A. In this case for claim construction, I consulted the specifications, which made it clear.

Q. Okay.

MS. RURKA: Let's turn to Page 8 of the exhibit, starting at Column 4, Line 50.

BY MS. RURKA:

Q. And what does this tell you that is the definition of TNFR:Fc?

A. Yes. So, I look at the second line here, which defines that TNFR:Fc, that's the same term that's used in the claims, a term which as used herein refers to etanercept. And then it goes on to describe etanercept the way we have it. It's a dimer of two molecules of the extracellular portion of the p75 receptor and so forth.

But the other main point is the last sentence in this paragraph, which states etanercept is currently sold by Immunex Corporation under the trade name Enbrel. So that made it very clear to me what is meant.

Q. Okay. So, let's take a look at Claims 11 and 35. We'll start with Claims 11 and 35 of the '182 patent and how they compare to Claim 1 of the psoriasis patents, and any of the three psoriasis patents, the relevant portions.

And can you -- why don't we walk through this, and can you just generally explain what you did here with Claims 1 and 35? What are we showing here?

A. So --

Q. I mean Claims 11 and 35. I apologize.

A. With Claims 11 and 35, I summarized the language that

refers to either the extracellular region of the insoluble p75 TNF receptor and highlighted that in green, and highlighted the part that refers to the immunoglobulin aspect, so the heavy chain other than the first domain in the constant region in blue just to have sort of an easier assignment.

And I -- since Claim 11 refers back to Claim 1, I summarized Claim 1 in brackets here in that it made it very clear that this is the p75 TNF receptor.

Q. Okay. Let's talk about the green part then first of each of these claims. And that is, for Claim 11, the extracellular region of the insoluble human -- and then from Claim 1 we know it's the p75 TNF receptor; and then for Claim 35, it's the extracellular region of the p75 human tumor necrosis factor receptor amino acid sequence encoded by the cDNA insert, which in Claim 30 and we understand is the p75 TNF receptor. Right, Doctor?

A. That's exactly right.

Q. How is that disclosed by Claim 1 of any of the psoriasis patents?

A. Claim 1 of the -- of all three of the psoriasis patents cite to a TNF receptor Fc, and the TNF receptor part, as I just discussed, I can say is from etanercept. And etanercept contains the extracellular region of the p75 TNF receptor, so it's the same molecule.

Q. Okay. And Claims 11 and 35 also require all the domains of the constant region of a human IgG1 immunoglobulin heavy chain other than the first domain of the constant region. Right, Doctor?

A. That's correct.

Q. And what do you understand that to mean via claim construction?

A. So, if I look at -- are you referring to Claim 1 of the psoriasis patent?

Q. Yeah. I'm referring to Claims 11 and 35. And what does the -- you understand there was a claim construction in this case of that part, the blue part of these claims. Right?

A. Yes.

Q. And what is your understanding of that construction?

A. That that is the same as the hinge-CH2-CH3 on the Immunoglobulin 1.

Q. Okay.

MS. RURKA: And I'll just note for the record that we agreed last night with plaintiffs that it would be exon-encoded hinge. I think that's the language we used, but okay.

BY MS. RURKA:

Q. So where is that disclosed then in the claims, Claim 1, of any of the psoriasis patents, Doctor?

A. Because the psoriasis patents in Claim 1 again refer to TNF receptor Fc or etanercept, all I had to do was look at the construction of the Fc portion of etanercept, which is the hinge-CH2 and CH3 domain. So it's the same domain.

Q. Okay. And so, the last part is, Wherein said protein specifically binds human TNF.

That provision is from the independent Claims 1 and 30, and is read into Claims 11 and 35. You understand that. Right, Doctor?

A. That's correct.

Q. Okay. And you understand that that means strongly and stably binds TNF, according to construction. Right?

A. I understand that.

Q. Okay. Where is that disclosed in the claims of the psoriasis patents?

A. Since the claims of the psoriasis patents cite to etanercept or the TNFR:Fc, that is a molecule that inherently and specifically binds human TNF. That's the whole point of etanercept. And so it's an inherent property of etanercept.

Q. And how do you know it's an inherent property of etanercept?

A. So, I would, of course, know this as a person of ordinary skill in the art, but I can also consult the packaging sheet for etanercept to further support this

point.
Q. Okay. Let's turn to DTX-44 in your binder. And, Dr. Blobel, what are we looking at here?
A. This is part of the packaging insert for etanercept.
Q. Okay. Did you review and rely on this in forming your opinions?
A. Yes, I did. And I would need to see the portion right below this.
MS. RURKA: Can we look at the indications and usage?
BY MS. RURKA:
Q. And what does this tell a person of ordinary skill in the art about the inherent properties of etanercept?
A. The very first sentence is, Enbrel or etanercept is a tumor necrosis factor blocker.
And so, that says that it binds specifically TNF-a, so it's an inherent property of etanercept.
Q. Okay.
MS. RURKA: And let's go back to JTX-41, which is again the Finck -- the psoriasis '631 patent.
BY MS. RURKA:
Q. And if you could turn to Page 8, Column 4, starting at Line 57. And this is right below what we just looked at.
And can you tell me what this teaches about the inherent properties -- this portion teaches about the

inherent properties of etanercept when it's used to treat psoriasis?

A. Yes. The sentence starting here, Because the p75 receptor protein that it incorporates binds not only to TNF-a but also to cytokine, it says that it binds specifically to TNF-a.

MS. RURKA: So if we go back to the slide DT -- I'm sorry -- DDX-1028.

BY MS. RURKA:

Q. So what about -- can you offer your summary of your opinion on whether the psoriasis patent claims rendered the asserted Claims 11 and 35 of the '182 patent obvious?

A. Yes. In my view, the psoriasis claims, in fact, since they claim etanercept, they render the extracellular portion of the p75 TNF receptor coupled to the IgG1 hinge-CH2-CH3 domain that is etanercept, so, it renders Claim 11 and 35 of the '182 patent obvious and invalid.

Q. Okay.

MS. RURKA: So let's turn to Claims 12 and 36, which are the last two asserted claims of the '182 patent.

BY MS. RURKA:

Q. And you prepared a chart again, Doctor. Is that right?

A. Yes, I did.

Q. Okay. This is DDX-1030. And each of these depends

from claim -- Claim 12 depends from Claim 11; Claim 36 depends from Claim 35. Correct?

A. That's correct.

Q. And so, you have additional elements here that you have highlighted. Can you describe what the additional elements are?

A. Yes. What I've highlighted here are essential components of making a drug, basically. So a drug has to have a pharmaceutical composition and it has to be in a pharmaceutically acceptable carrier material.

And in Claim 1 of the psoriasis patent, there is a reference to a method of treatment.

Q. And how does that relate to the elements of Claims 12 and 36 of the '182 patent?

A. To be able to use etanercept for treatment of patients, it would be obvious that it has to have an appropriate pharmaceutical composition and a pharmaceutical -- and be in a pharmaceutically acceptable carrier material.

Q. Okay.

MS. RURKA: So let's turn to the '522 patent.

BY MS. RURKA:

Q. And have you prepared a chart comparing the asserted claim of that to the psoriasis patents?

A. Yes, I have.

Q. Okay. Let's --

MS. RURKA: This is DDX-1031.

BY MS. RURKA:

Q. Okay. So there are a lot of words on this page. It's Claims 3 and 8. Can you just generally talk about what the green part is again?

A. Yeah. I highlighted the language in green from Claim 1 because it is rather cumbersome, but I can say that this is the same as what we just discussed previously. It's the p75 extracellular domain of the TNF receptor is the green part, and the blue part is the portion of the IgG that consists of the hinge-CH2 and CH3 domain. So that's how it's summarized by color-coding.

Q. Okay. Is that -- how does the psoriasis patents relate to that, those two portions of these claims?

A. Since the psoriasis patents claim etanercept, it's the same molecule.

Q. Okay. And in the orange here we have some extra elements. Part (a) would be, Culturing a host cell comprising a polynucleotide, wherein the polynucleotide encodes a protein; and then, Purifying an expression product of the polynucleotide from the cell mass or the culture medium.

And those are additional elements that are in the '522 patent claims. Right, Doctor?

A. That's correct.

Q. Would those be obvious in view of what is disclosed in the psoriasis -- or what is the claimed in the psoriasis patents?

A. Yes, that would have been obvious.

And so, to just describe this briefly, the main difference between the '522 and the '182 is that the '522 patent contains a method of production.

And, of course, if you would like to generate something like etanercept, you would have to produce it, meaning you would have to culture a host cell comprising a polynucleotide, very similar to the demonstrative that I showed earlier, wherein the polynucleotide encodes a protein that consists of etanercept; and you would have to purify the expression construct and product from the cell or culture medium.

So those two points I had summarized on my earlier demonstrative what you would need to do to make a medicine. It's summarized here and, of course, it's very obvious, and also obvious to me, that if you were to make etanercept, you would have to go through these steps.

So that's an obvious -- that's obvious that one would have to do this.

Q. Okay.

MS. RURKA: And then let's turn to the last asserted

claim, which is Claim 10 of the '522 patent.
BY MS. RURKA:
Q. And that one depends from Claim 8, so it contains all the elements of Claim 8, and it adds the host cell being a CHO cell. So what is a CHO cell, Doctor?
A. A CHO cell was one of the major cell types that was used by scientists at the time and, so, it would have been an obvious choice for that reason to use to make etanercept with.
Q. Okay. So can you provide a summary of your opinion with respect to double-patenting of the '522 patent claims in view of Claim 1 of any of the psoriasis patents?
A. The '522 patent is invalid in light of Claim 1 of any of the psoriasis patents. That's my opinion.
Q. Okay. So let's -- so that's the psoriasis patents.
Why don't we move on to double-patenting on the Jacobs patents, which is the second set that you have listed here. And can we turn to JTX-42 in your binder?
And, Doctor, what is this document?
A. This is the Jacobs patent. It's the '690 patent filed by a Cindy Jacobs and a Craig Smith, also from the Immunex Corporation.
Q. And what is this generally directed to?
A. This is generally directed to etanercept basically, and it's used for treatment of TNF-dependent pathologies.

Q. Okay.

MS. RURKA: So let's turn to Claim 3, which is on page -- thank you. I didn't know what page it was on.

BY MS. RURKA:

Q. The Claim 3 of the '690 patent, is this the one you relied on in forming your opinion?

A. That's correct.

Q. Okay. So why don't we talk through this claim. Can you generally give us an idea of what the claim is about and what the pieces of the claim are?

A. Yes, I can. It discusses a method for lowering the levels of active TNF in a mammal in need thereof, which comprises administering to said mammal a TNF-lowering amount of a chimeric antibody comprising the TNF receptor comprising the sequence of amino acids 3 to 163 of SEQ ID NO: 1 fused to the constant domain of an immunoglobulin molecule.

Q. So what does "chimeric antibody" mean?

A. A chimeric antibody in this case refers to an antibody in which a receptor is coupled to a part of an IgG molecule, so it's a chimeric fusion protein.

Q. Okay. And what does amino acids 3 through 163 of SEQ ID NO: 1 refer to?

A. That is, as the wording in the sentence also indicates, that's a sequence. So the sequence is comprised

within a larger sequence. The sequence 3 to 163 is comprised within the extracellular domain of the p75 TNF receptor.

Q. Okay. And then the last part says, Fused to the constant domain of an immunoglobulin molecule. And what does that refer to?

A. That refers to the hinge-CH2 and CH3 on the immunoglobulin molecule.

Q. Okay. How did you determine what this claim means?

A. In this case, I had to consult the specifications to undergo a claim construction.

Q. Okay. Thank you.

MS. RURKA: So let's turn to Page 3 of JTX-42, which is still the '690 patent.

BY MS. RURKA:

Q. And what is this Figure 1 showing?

A. This Figure 1 is essentially etanercept or it is etanercept. So you can see here the soluble portion, the extracellular domain of the p75 TNF receptor and on the lower side you can see exactly the hinge-CH2 and CH3 domain of a human IgG basically. And this would be one copy in the end in the etanercept itself or the recombinant human TNF receptor/Fc protein. This forms a dimer with two arms of the TNF receptor coupled again to the hinge-CH2 and CH3 domain. So this is etanercept.

Q. Okay. And let's turn to Page 16 of JTX-42. And let's take a look at Example 2. And what is Example 2 related to, Doctor?

A. So, Example 2 describes the construction and expression of soluble human TNF receptor:Fc, and it describes the recombinant protein, the TNFR:Fc. It cites very clearly to Figure 1 so that made it clear to me what it is. And it also has sequence information that further confirms this point.

Q. Okay. And let's turn to Example 4, which is on Page 18. And what is Example 4 related to, Doctor?

A. Example 4 is related to the usage of the TNFR etanercept in this case and there are really two points I'd like to emphasize. One is that this is supposed to be used for arthritis and for rheumatic or inflammatory condition.

And then that's further emphasized at the end of the first paragraph where the TNF receptor, the recombinant human TNFR:Fc, which I just defined as etanercept, is used to suppress the effects of antigen-induced arthritis in rats.

Q. Okay. And you've looked at Examples 5 and 6 in this patent specification. Correct?

A. Yes, I have.

Q. And what are those two examples related to?

A. They're also related to treating arthritis,

inflammatory arthritis, essentially just different forms of it.

Q. Okay.

MS. RURKA: And can we go to Page 13, Column 7, starting at Line 54 through the end of that paragraph. Just through the end of the paragraph. There you go.

BY MS. RURKA:

Q. And here it says, this is part of the specification, One specific example of a TNFR:Fc fusion protein is disclosed in SEQ ID NO: 3 and SEQ ID NO: 4. And what protein is that?

A. It's etanercept.

Q. Thank you. Let's take a look at the file history. You looked at the file history to conduct your claim construction of this claim. Isn't that right?

A. That's correct.

Q. Okay. So let's take a look at that and let's turn to DTX-55 in your binder.

And what is this, Doctor?

A. This is a file history of the '690 patent which was called the '229 at the time, and it is related to using this as a method for treating TNF-dependent inflammation.

Q. So this is a portion of the '690 patent file history. Is that right?

A. That's what it is.

Q. Okay. So let's take a look at the second -- I'm sorry -- Page 5 of these remarks.

MS. RURKA: And pull up -- yes, that paragraph there right before the rejection response.

BY MS. RURKA:

Q. So what are they telling -- you understand they were responding to a rejection from the Patent Office to their claims. Immunex was responding to the rejection of the patent from the Patent Office to their claims. Right?

A. Yes, I understand that.

Q. Okay. And what did they -- how did they respond to the Patent Office?

A. They responded essentially by emphasizing the usefulness of this to treat arthritic condition in humans and that's shown in the sentence starting here:

Indeed, Dr. Moreland declares that the recombinant soluble TNFR:Fc, which is etanercept, fusion protein is well tolerated and the rheumatoid arthritis patients showed trends of improvement in painful and swollen tender joint counts and biological indicators of inflammation.

So this very clearly showed a usage for etanercept to treat rheumatic diseases.

Q. Okay. And the last sentence says: Clearly the claimed method possesses patentable utility.

Do you see that?

A. Yes.
Q. What are they telling the Patent Office about what their claimed method is?
A. The claimed method is to treat patients suffering from inflammatory conditions such as rheumatoid arthritis with etanercept, and they claim that this is patentable.
Q. Okay. So let's do the comparison of the asserted claims of the '182 patent to Claim 3 of the Jacobs '690 patent under your construction, Doctor. Okay.
A. Yes.
Q. And I know Dr. Wall provided a different construction and we can get to that when you're talking about your obviousness opinion. Is that all right?
A. That's fine.
Q. Okay. So let's go to DDX-1035. And again, you've color coded the chart here, Doctor. Is that right?
A. Yes, exactly the same as I did earlier. We've got the green extracellular portion of the p75 TNF receptor and in blue it's the Fc portion of an IgG1.
Q. Okay. And where is the p75 TNF receptor extracellular region claimed in Claim 3 of the Jacobs '690 patent?
A. The Jacobs '690 patent Claim 3 describes a TNF receptor comprising the sequence of amino acids 3 to 163 of SEQ ID NO 1. So, because of the word "comprising," this is

a sequence that is contained in the full length extracellular region of the p75 TNF receptor.

Q. Did the art in 1990 teach a person of skill to use the entire extracellular region of p75 receptor?

A. Yes, it did.

Q. Okay. So let's turn to JTX-65 in your binder. And can you identify this patent, Doctor?

A. Yes, I can. This is the '760 patent by Craig Smith at Immunex, so, it's what we refer to as the Smith patent.

Q. Okay. And do you know how this relates to the '690 patent?

A. The two are related to one another and the '760 patent is a precursor of the '690 patent.

Q. Okay. Let's turn to Page 9 of JTX-65 and let's take a look at Column 2, Line 36, to the summary of the invention. And can you just generally discuss what they're summarizing their invention is in the '760 patent?

A. Yes. In a very general sense, they are describing isolated TNF receptors and DNA sequences and how to use them basically to make fusion proteins such that you can make biologically active TNF receptor molecules.

Q. And which TNF receptor is the subject matter of this Smith '760 patent?

A. So, this is the Smith patent, obviously from Immunex, and a major breakthrough actually was the publication of

the p75 TNF receptor sequence by Dr. Smith in 1990.

Q. Okay. So let's turn to Page 4. Does this -- this discloses that sequence as well?

A. Yes, it does.

Q. Okay. So, we're at Figure 2A and Page 4 of the '760 patent. And why don't you give -- why don't we orient the Court first. Can you just tell us what we're looking at here, what all these letters are?

A. Yes, I can. And this is one of the cumbersome ways that scientists like to present their sequences. It's not that hard to understand. Basically, you have both the DNA sequence, which is the single-letter code with four different letters, where a triplet will encode an amino acid. And then you have the amino acid shown in the three-letter code that's tried to match up here. But basically you have three codons of DNA encoding for one amino acid residue, and that's the genetic code which is actually quite easy to see on this figure.

Q. Okay. So, we have multiple pairs of rows here so why don't we pull up one pair and we'll walk through just which parts are which.

MS. RURKA: Can you pull up the one that has the number "222" next to it? Thank you, Mr. Haw.

BY MS. RURKA:

Q. Okay. So we have two -- a pair of rows here.

There's a top row and a bottom row with different letters. Right?

A. That's correct.

Q. Okay. What is the top row?

A. So this is really quite a nice self-explanatory way to show the genetic code. Again, on top you can see the DNA sequence. So, for instance, these three "Cs" over here encode for the protein -- the amino acid, which is shown on the lower row, proline, and "TAC" will encode for "TYR", which is tyrosine.

And this is essentially how scientists will present a protein that's been cloned because it's just an unambiguous identifier. You have both the DNA sequence and that gives you the exact series and order of beads on a string of the amino acids. That's what this is.

Q. Okay. So the bottom row then is the amino acid sequence. Is that right?

A. That's correct. And that's why the numbers are different. You have 222 referring to the start of the DNA sequence up here, and the 23 essentially refers to the start of, in this case, the mature protein.

Q. Okay. So, why don't we just talk really briefly about the numbers a little bit more carefully.

Is it correct that that number 222 is -- refers to the C, which is the last letter on the DNA sequence there

that's shown in this row? Is that right?
A. Yes. That's exactly correct. And the 23 would refer to the tyrosine at the end of this row. And so, if, as is also in the specifications of this patent, somebody indicates a sequence length or an end for a sequence, you would know exactly where to find that.
Q. By the number?
A. By the numbers. So, if it's 235, you could go there and say this is where a protein stops.
Q. Okay. Let's turn to Page 13 then of JTX-65, starting Column 9, Line 23.
MS. RURKA: And if you can pull up that provision.
BY MS. RURKA:
Q. And here we -- here we have -- this is what this says, The resulting protein is referred to as a soluble TNFR molecule which retains its ability to bind TNF. A particularly preferred soluble TNFR construct is TNF r-delta 235, the sequence of amino acids 1 through 235 of Figure 2A which comprises the entire extracellular region of TNFR, terminating with ASP-235 immediately adjacent the transmembrane region.
So that's a lot of words. Can you kind of break it down in layman's terms as to what they're describing here as the particularly preferred portion of the TNF receptor to use?

A. Sure. It's a lot of words. It's quite simple in the end. So first of all, I'd like to note that the number 235 is mentioned three times, so that's where the sequence stops. And what's conceptually important is that it stops immediately adjacent to the transmembrane domain.

So if you think back to the demonstrative with the scissors I showed you earlier, if you would cut the molecule off such that you release the entire business end, that's exactly where you would cut it off, at this 235. And it generates a soluble form of the receptor so that's something that can actually go away from the cell barrier and bind TNF and prevent it from binding to cells.

So really because the Jacobs patent builds on this one, I think in my view, this -- or this just very clearly describes the type of construct that is meant in the Jacobs patent, and that's exactly the part that is in etanercept. And it's the one as a POSA even that I would choose because it makes the most sense to use the entire extracellular domain.

Q. Okay. So let's talk -- turn back to DDX-1035, and we'll talk about the second part of the claim which is the blue part. And where is the blue part in claims -- all the domains is generally the blue part of Claims 11 and 35. And where is that disclosed in Claim 3 of the Jacobs patent?

A. It's disclosed in the part of the sentence that's highlighted in blue, so, it's the constant domain of immunoglobulin and molecule. And again, recall that I consulted the figure in claim construction where it very clearly shows me that it's the hinge coupled to the CH2 and CH3 element.

Q. Okay. And which type of immunoglobulin molecule would a person of ordinary skill in the art have selected as an obvious choice to use for this construct of Claim 3 of the Jacobs patent?

A. So, obvious choice would have been an immunoglobulin in one. There are a number of different immunoglobulins but that's the one that's by far the most common. And we have the most IgG1, so, it was therefore also best understood and would have been an obvious choice for that reason.

Q. And you said "we have the most IgG1." What did you mean by that?

A. Yes. I'm sorry. I mean that in our bodies and in circulation we, of course, have different types of immunoglobulins. But the concentration of the IgG1 is the highest and that's why it is -- was the best studied and best understood and would have been an obvious choice.

Q. Okay. So let's go back to JTX-65, Page 13. Again we're in the Smith '760 patent. And let's go to Column 10,

Line 57.

And what -- so here it says, For example, chimeric TNFR IgG1 may be produced from two chimeric genes.

And what is this telling you -- telling a person of ordinary skill in the art in 1990 about what sort of immunoglobulin to use?

A. So, in this case it also simply spells out that the TNF receptor should be fused in this case to an IgG1.

Q. Okay. Let's go back to DDX-1035. And so the last part of these two claims is, Wherein said protein specifically binds human TNF. And where is that disclosed in Claim 3 of the Jacobs '690 patent?

A. Claim 3 of the Jacobs '690 patent calls for a method in which a TNF-lowering amount of etanercept is given to a mammal. And so it's obvious then -- I'm sorry, this is an inherent property, of course, of a TNF receptor, that it will bind to TNF. So it's an inherent property of etanercept, that it will do this.

Q. Okay. So let's turn to Claims 12 and 36, and we'll do the same analysis as we did with the psoriasis patents.

As you recall, Claim 12 and 36 both talk about a pharmaceutically-acceptable carrier material and a pharmaceutical composition. And how is that -- where is that disclosed in the Jacobs '690 patent, Claim 3?

A. It's essentially the same analysis because the Jacobs

also covers etanercept. It's obvious that you would have to prepare it and put etanercept in a pharmaceutically-acceptable carrier material. It's an obvious component.

Q. Okay. And then let's turn to the claims of the '522 patent, and we'll take a look at Claims 3 and 8. And again we're looking at the same chart as before, but we have -- as before with the psoriasis patents, but instead we have Claim 3 of the Jacobs '690 patent.

How does Claim 3 of the Jacobs '690 patent relate to and render obvious the claims of Claims 3 and 8 of the '522 patent?

A. So my analysis is exactly the same. I could go through it but I can also simply say my analysis is the same as for the '182 patent and Claim 3 of the Jacobs patent renders the Claim 3 in aids of the '522 patent invalid.

Q. Is it correct that the methods of making are the same methods that you described with respect to the psoriasis patents?

A. Yes, that's correct.

Q. Okay. And then finally, let's look at Claim 10, and that is CHO cell. And does your analysis differ in any respect with the CHO cell as it does with the psoriasis patent claims?

A. It does not. The CHO cell was a very widely-used cell at the time. Still is. Would have been an obvious choice to make.

Q. Okay. Thank you, Doctor.

MS. RURKA: I'm not sure if it makes sense to take an afternoon break now or --

THE COURT: We can do that. It's 3:00. No. That's fine. If it's a good time for you to break, we can take our break for ten minutes. I plan to go until five today so this is a decent time to do that.

MS. RURKA: Okay.

THE COURT: And then you're going to continue with this witness you think until the conclusion, or how much longer do you think?

MS. RURKA: It will probably be maybe another hour.

THE COURT: Okay. So let's take a break here. If we need a five-minute break before we start the cross, we'll do that as well, too. Okay. Thank you. You may step down from the stand. Thank you.

(A recess is taken.)

THE COURT: Have a seat, everyone. Let's continue.

MS. RURKA: Thank you, your Honor.

BY MS. RURKA:

Q. Doctor, so let's move to your obviousness opinion. And we talked earlier about the level of ordinary skill in

the art and that's the perspective you applied here as well, Doctor?

A. Correct, exactly the same.

Q. Okay. So let's move on to the scope and content of the art. As of August 1990, in informing your opinions, did you consider that?

A. Yes, I did.

Q. Okay. First of all, let's start with TNF and the TNF receptors, because that's kind of the topic of the day.

What was the level of interest in TNF as a target in August of 1990?

A. It's fair to say that it was really a very hot target, so, the level of interest was tremendous also in major companies involved in biotech.

Q. Do you have any references that can reflect the state of the art at the time with respect to TNF?

A. Yes, I do.

Q. Okay. Let's take a look at DTX-75, which is the Brennan 1989 paper. And can you identify this publication?

A. This publication is in a very highly-respected journal called The Lancet, the medical journal. It was published in July 1989 and it is related to the function of TNF. The author, first author was Fionula Brennan. And the title of the paper is *Inhibitory Effect of TNF-Alpha Antibodies on Synovial Cell Interleukin-1 Production in*

Rheumatoid Arthritis.

Q. Doctor, did you rely on this in reaching your opinion regarding what the state of the art was in 1990?

A. Yes, this is a very good example. And if we turn to the -- if I turn to the summary actually, I can highlight some of the key points of this particular paper.

Q. Please do.

A. The summary outlines the essence of this study, which is on the effect of tumor necrosis factor alpha antibodies on synovial cell interleukin-1 production that was investigated in patients with rheumatoid arthritis, seven patients, and in seven patients with osteoarthritis. Interleukin-1 is another inflammatory cytokine so these are indicators for inflammation.

And I would then also like to highlight the last sentence, which is the summary of this manuscript. And it states, In rheumatoid arthritis, TNF Alpha may be the main inducer of IL-1 -- again, another pro-inflammatory mediator -- and anti-TNF alpha agents may be useful in treatment.

So, a paper in a major medical journal in July 1989, and this was one of several.

Q. And what is this telling you? In layman's terms, what is this teaching a person of skill in the art?

A. It teaches that rheumatoid arthritis, which is a

debilitating autoimmune disease, that TNF may be a major target for treatment of rheumatoid arthritis and that anti-TNF agents may be very useful in that treatment. So it provides a very strong incentive to identify good or better inhibitors of TNF-a.

Q. Okay. So let's turn to JTX-62 in your binder. And this is a patent application, European Patent Application. And did you review or rely on this, Doctor, in informing your opinions?

A. Yes, I did.

Q. Can you just generally describe what this patent application is directed to?

A. Yes. This is a patent application that was filed in 1988, in September of 1988, and it's directed to tumor necrosis factor inhibitory protein and its purification. And it is directed essentially to the same idea of using TNF blockers to treat inflammatory diseases.

Q. Okay. And what was the date this application was published?

A. So it was published in -- the date of filing was in 1988.

Q. And I'm sorry. If you --

A. September 1988.

Q. And if you go down to "date of publication of application," what's the date there?

A. On the 22nd of March, 1989.

Q. Okay. And let's turn to Page 2 of JTX-62 and take a look at Lines 16 through 34 -- I'm sorry, 16 through 24.

Okay. So, can you explain what this portion of the specification of this application is teaching with respect to TNF?

A. Yes. So, one reason to highlight this section is to further emphasize how well it was recognized that TNF is a target. Let me just read these lines. Quite clearly both TNF-alpha and TNF-beta have also effects which can be extensively deleterious. There is evidence that overproduction of TNF-alpha can play a major pathogenic role in several diseases.

And then without further reading, you know, all the details, I would just like to highlight rheumatic diseases, which is a major, major disease area caused by TNF.

And then there are graft-versus-host disease mentioned here. And it's also called "anorexia," caused by a different effect of TNF. But the main point is that rheumatic diseases were recognized as a TNF-dependent pathology that was in need of TNF inhibitors.

Q. And does this publication teach you methods for addressing the overproduction of TNF?

A. Yes, it does.

Q. What does it teach?

A. It teaches to use the soluble extracellular domain of TNF receptors for this purpose.

Q. Okay.

MS. RURKA: Let's go to Lines 57 through 58, on Page 2 as well.

BY MS. RURKA:

Q. And what is this telling you down here? The present invention provides TNT inhibitory protein, salts, functional derivatives and active fractions thereof, which can antagonize the effects of TNF.

A. Yes. So it tells you that -- and this should of course be TNF not TNT -- that TNF inhibitory protein could be used to block the effects of TNF such as in rheumatoid arthritis.

Q. What was the level of TNF receptors as of August 1990?

A. The level of interest?

Q. Yeah, the level of interest. I apologize. Yes.

A. The level of interest in TNF receptors was very high at the time, and different groups coming from very different directions were interested in this area.

MS. RURKA: Okay. So let's take a look at DDX-1042.

BY MS. RURKA:

Q. And can you discuss the institutions on here and what they were doing in this area?

A. Yes. I've highlighted three major institutions that were, and in part still are, active in biotech, so there's of course Genentech, which was interested. There was Immunex that we've begun discussing. There was Roche that we've also discussed. And the patent that we were just looking at was from the premiere science institution in Israel, the Weizmann Institute.

Q. Okay. And that was the Wallach '378 publication that came out of that?

A. Yes, that was exactly the patent that we just looked at. And then subsequently papers were published to follow up on that work.

Q. Okay. So why don't we take a look at a timeline and kind of just walk through what the development of TNF receptors was before August of 1990, and this starts with DDX-1043.

And, Doctor, why don't you -- can you tell us kind of the first major development in TNF receptor research that occurred before August 1990?

A. Yes. So what I've done here is essentially summarized the timeline and the different types of efforts that were pursued at the time.

We just discussed the September 1988 Wallach patent publication, that's JTX-62. And in 1989 that was followed by a publication by Engelmann, who is one of the authors in

the patent, 1989. That's JTX-46. And in January 1990 there was another paper with Engelmann as first author, that's JTX-47.

The topic of these papers was the identification of inhibitors of TNF, and those were the extracellular domains of the TNF receptors is what they realized later.

Q. Okay.

A. And actually -- I'm sorry -- they realized in these papers they spelled this out.

Q. Okay.

MS. RURKA: So let's go to DDX-1044.

BY MS. RURKA:

Q. What was the next step or major milestone in research relating to these TNF receptors?

A. The second type of effort was directed towards understanding what these TNF inhibitors were. And without going into detail, there was a series of two papers actually, September 1989, Hohmann, JTX-63, and April 1990 Brockhaus, JTX-22, that used antibodies and cell types to characterize the different types of TNF receptors. And they concluded at the time that there are at least two different types.

MS. RURKA: Let's go to DDX-1045.

BY MS. RURKA:

Q. And can you discuss the next major milestone in this

research?

A. Yes. The disclosures of papers that we just discussed were focused on inhibitors, and so that was a very important concept here.

But the other way that scientists were addressing TNF receptors was by trying to clone them. And in this particular case, the sequence of the p55 TNF receptor was published simultaneously in this same issue of a high profile journal that's called Cell.

In 1990 there was a paper by Schall, JTX-64. That was from Genentech. And then in the same issue a paper by Loetscher, 1990. That's JTX-21. And that was from Roche.

Q. So is it correct to say that both Genentech and Roche, the inventors, published on the same day the -- in the same issue, the amino acid sequence for the p55?

A. Yes, simultaneous publication.

Q. Okay. What was the next milestone with respect to TNF receptor sequences?

A. The next milestone was reached shortly thereafter. Again, the previous studies had identified two different types of TNF receptors. So one had now been cloned, the p55.

The second one, the p75 TNF receptor, was published by Smith from Immunex in 1990. And that's JTX-24. And that was also the basis for the Smith '760 patent, which is

JTX-65, and which we've already consulted a few times.

And I think it's quite evident actually, looking at this demonstrative, that not only was the level of interest in TNF and TNF receptors very high, but it was also building sort of from some of the first publications outlining this to then just a flurry of activity, which continued also, of course, after the filing date of the patents, or the date that we're using now, which is August 1990.

Q. Okay.

MS. RURKA: And let's go to DDX-1048.

BY MS. RURKA:

Q. And that's reflected here at the end. Right?

A. That's correct.

Q. Okay. So we had talked earlier about generally finding TNF inhibitory finding proteins, and did the art identify any purpose in developing the TNF receptors here?

A. Yes, it did.

Q. Okay.

MS. RURKA: Let's pull up DDX-1049 -- 1048. I apologize. I'm getting my numbers wrong.

BY MS. RURKA:

Q. So, you have some several quotes here from articles. Can you just go through and explain what these are teaching?

A. Yes. So I put this together to quote some of the articles that we just showed on this timeline to emphasize the fact that people actually realized what this was useful for.

The Wallach patent says, There is therefore a necessity in finding out ways to eliminate or antagonize endogenously formed or exogenously administered TNF-a.

Therefore the need was felt for development of biological agents which could similarly antagonize the deleterious effects of TNF-a.

Q. And that's JTX-62 at column 2, Lines 24 through 31 for the record.

A. Yes.

Q. Please continue.

A. Thank you. The Engelmann publication in 1990, which is JTX-47 at Page 6, spells out that "Detailed information on the structure of the receptors and knowledge of ways to produce them in a bioactive soluble form could provide us with inhibitory molecules which might act as therapeutic agents for suppressing overresponse to these cytokines in disease."

And then the third example I'm showing here is the Smith 1990 page, a major breakthrough, JTX-24 at Page 4. "Soluble recombinant forms of this receptor may also be produced to explore the clinical value of TNF inhibition in

pathological settings."

And of course, Dr. Smith further pursued this as we know, to -- yes.

Q. Okay. So why don't we talk about Dr. Smith's work. And did Dr. Smith recommend using -- doing a fusion protein of a TNF receptor with an IgG1?

A. Yes.

Q. Okay.

MS. RURKA: Let's turn to the '760 patent. That's JTX-65.

BY MS. RURKA:

Q. And we had looked at this earlier, and let's take a look at the fusion protein that Dr. Smith had recognized. Let's turn to Page 9 column 2, Line 67.

Actually, why don't we talk first about what they were teaching was the use for these receptors. Why don't we talk about that.

MS. RURKA: And we'll go to column -- Page 9, Column 2, Line 67.

A. Yes.

Q. And what does Dr. Smith teach here about the usefulness of these TNF receptors -- or the TNF receptor p75 that he was discussing?

A. Yes. As I was also discussing earlier, there were efforts identified TNF inhibitors, and Dr. Smith spells

this out very clearly here: Because of the ability of TNF to specifically bind TNF receptors, purified TNF receptor compositions will be useful in diagnostic assays for TNF, as well as in raising antibodies to TNF receptor for use in diagnosis and therapy.

And now comes the key sentence in this context. "In addition, purified TNF receptor compositions may be used directly in therapy to bind or scavenge TNF" -- there's the word scavenge that I also used earlier -- "thereby providing a means for regulating the immune activities of cytokine."

Q. So, let's talk about the construct -- one of the constructs that he recommends using.

MS. RURKA: And if we could turn to Page 13 at Column 10, Line 53.

BY MS. RURKA:

Q. Can you just go over what he is recommending as a construct for the p75 TNF receptor to use -- to scavenge TNF?

A. Yes. So, here is the idea of combining, of making a chimeric molecule that has TNF receptor sequences substituted for the variable domain of an immunoglobulin molecule, that can be the heavy or the light chain. And he cites several examples.

One example would be the chimeric TNFR IgG1 that we

discussed earlier in the context of saying that IgG1 is important; maybe produce from different chimeric genes which can contain the TNF receptor on the heavy or the light chain.

He then further goes on to point out a very important property of such a TNF receptor IgG fusion protein, and that is that such polyvalent forms of the TNF receptor may have enhanced binding affinity for TNF ligand. And what he means here is the concept also of avidity that I will get back to later, but that's an important property of receptor Fc fusion proteins.

Q. So you prepared a slide that kind of explains what Dr. Smith's structure looked like in the '760 patent?

A. Yes, I did.

Q. Okay.

MS. RURKA: Let's go to DDX-1049. Okay.

BY MS. RURKA:

Q. So can you explain what he was suggesting you could do as one fusion protein for a p75 TNF receptor in an immunoglobulin?

A. Yes, I can. I actually just read this paragraph or parts of it.

And so what I'm showing here is the immunoglobulin structure that I described earlier. And he recommends substituting the variable domain, which is the light blue

VL and VH part that I also described earlier, of both immunoglobulin molecules with the TNF receptor sequences, and that would result in a molecule as diagrammed on the right here where essentially the blue parts, the variable parts, have been replaced with the receptor.

One advantage of taking this approach is it's actually quite hard to make antibodies against TNF, for example, and by taking the business end of a TNF receptor that a POSA would know, and he knew, binds TNF, you essentially instantly make a TNF-binding molecule and drug. This was a great idea.

Q. Okay. So, earlier we had talked about Dr. Wall having an opinion about the construction of Claim 3 of the Jacobs '690 patent. I want to bring that back up here because it relates to this.

What is your understanding of Dr. Wall's construction of Claim 3 of the Jacobs '690 patent.

A. Let me just preface that by saying that I disagree with Dr. Wall on this point and, as I outlined earlier, I think Claim 3 of the Jacobs patent very clearly describes etanercept. But Dr. Walls' construction is essentially like the one that I'm showing here.

So, it is the extracellular parts of the receptor that is attached to the CH1 domain of immunoglobulin molecule, both the heavy and the light chain.

Q. Okay. And so, in an obviousness analysis you're required to compare the claims, the asserted claims, to the prior art.

So, have you done that sort of comparison to the structure that Dr. Smith has disclosed here?

A. Yes, I have.

Q. Okay.

MS. RURKA: Let's turn to DDX-1051.

BY MS. RURKA:

Q. And how do these two structures differ?

A. The structures differ, as you can see here, by the fact that the Smith patent construct in fact contains a light chain which the etanercept construct does not.

And in addition, there is also a CH1 domain that is here and is removed in etanercept. So, those are the two key differences.

Q. So would a person of ordinary skill in the art view the Smith construct as being the one to use?

A. Not necessarily, because there were other studies going on at the time that would have provided an incentive and great ideas actually to change this and improve on it and turn it into something better --

Q. Okay.

A. -- like etanercept.

MS. RURKA: So let's turn to DDX-1052.

BY MS. RU RKA:

Q. And so we'll talk a little bit about the -- I'm sorry.

MS. RURKA: Let's go to 1053.

BY MS. RURKA:

Q. And we'll talk about fusion proteins generally and what the state of the art was in August of 1990 with respect to fusion proteins.

So, why don't you start with what you have here on DDX-1053 and describe what you're showing here.

A. What I'm showing on DDX-1053 is a summary of a major breakthrough, a paper published by Dr. Capon in 1989. Dr. Capon is here today. This was a paper in one of the top biomedical journals, in Nature.

And Nature has a category that's referred to as an article, which was really the top of the top. So this was an article in Nature, and it described the breakthrough concept that you can make a so-called immunoadhesin where you couple the extracellular domain of a receptor to an immunoglobulin molecule.

And in this paper, he actually describes going through different permutations of this type of a construct. One of them, shown on the left, resembles the construct that Dr. Wall proposes in his claim construction for the Jacobs patent, and that also includes the light chain.

However, and I will read from Dr. Capon's paper, "We have therefore produced a number of CD4-immunoglobulin hybrid molecules, using both the light and the heavy chains of immunoglobulin, and investigated their properties. We have named one particularly interesting class of these CD4-immunoglobulin hybrids 'immunoadhesins' because they contain part of an adhesive molecule linked to the immunoglobulin Fc effector domain."

And I'm showing an immunoadhesin on the right here. One of the key features actually that was part of this paper was that this worked without the light chain.

So Dr. Capon would have taught to remove the light chain.

Q. Okay. And what is -- just to orient the term, what is CD4?

A. CD4 is a receptor for the AIDS virus. And at the time that was the motivation to make this type of a molecule, was to treat HIV patients.

Q. Okay. So I think you testified that Dr. Capon's construct still had a CH1 domain. Right?

A. That's correct.

Q. And that is different than etanercept, which did not have CH1 domain. Is that correct?

A. That's correct.

Q. Okay. Would there have been a reason to remove the

CH1 domain?

A. Yes. And as is often the case in science, scientists constantly try to improve the constructs and the things that they make and work with, and precisely that happened here.

So Dr. Capon had the concept, this was a major breakthrough of a highly recognized and cited paper, but it was actually very rapidly built upon and improved upon by others and also by his own group.

Q. Okay.

MS. RURKA: So let's take a look at JTX-25. We'll start with that.

BY MS. RURKA:

Q. And what is this paper, Doctor?

A. This is a paper also in the highly-respected journal Nature by Andre Traunecker, and it describes a highly efficient neutralization of HIV with recombinant CD4 immunoglobulin molecules. So this was a paper that was showing a similar type of construct.

Q. And when was this published?

A. This was published in Nature, I believe it was in May 1989.

Q. Okay. And what did -- did you consider and rely on this in forming your opinions in this case?

A. Yes, I did.

Q. Okay. And what does Dr. Traunecker teach here about these fusion proteins?

A. The essence of this paper is summarized in the last sentence of the abstract. So the abstract, of course, summarizes the essence of a study.

And in this particular study, I will read the last sentence to you. "Deletion of the CH1 domain may allow the association and secretion of heavy chains in the absence of light chains," so that's something we've already discussed, "and we suggest that the basic design of our constructs may be generally and usefully applied."

So they also remove the light chain, but the key instruction, or the key teaching from this paper is that deletion of the CH1 domain may be generally and usefully applied.

Q. Okay. So let's take a look at what the structure of this molecule looked like.

MS. RURKA: And we'll go to DDX-1054.

BY MS. RURKA:

Q. And what are you showing here on DDX-1054?

A. So I've prepared a very simple demonstrative to show that the CH1 domain has been removed in the Traunecker construct.

Q. As opposed to the Capon construct?

A. As opposed to the Capon construct.

Q. Okay. And did anyone else follow Traunecker's example?
A. From then on, the major publications and examples that I saw and found in citing all followed this advice.
Q. Okay. Why don't we talk through each of these.
First of all, did anyone ever make the Smith structure or any CD4 like the Smith structure?
A. Not that I'm aware of. Dr. Capon describes the attempts to make them in his paper, but then he publishes this because it's much easier to make. Removal of the light chain gives you a construct that's easier to synthesize and works and has many advantages.
Q. Okay. So, next to the Traunecker figure we have Figure 1 of Byrn 1990, which is JTX-56.
What is the Byrn Group?
A. The Byrn Group is Dr. Capon's group.
Q. And what sort of constructs did they make in JTX-56?
A. You can see that the CH1 domain is also missing.
Q. Why is the CD4 -- that's a CD4 protein. Right?
A. The orange part is the CD4 protein.
Q. And why is it smaller than the one you see in Traunecker?
A. The CD4 protein that Dr. Capon and Dr. Traunecker used was the full length extracellular receptor. But Dr. Capon also used a truncated form of this receptor.

And in this particular case, through experimental evidence, this is not something you could predict, but through experimental evidence established that a truncated shorter form of the CD4 also works. And hence, he continued working with that. And that's why I showed it as a truncated version here.

Q. Okay. So let's talk about the pCD4 E Gamma-1 of Seed '262 publication at JTX-57. And can you just describe what that construct is?

A. This was a patent application that also included Fc fusion proteins between CD4 and IgG1 fused at the hinge, followed by CH2 and CH3. So this is a construct that was published in a patent application by Dr. Brian Seed.

Q. And just to orient the Court on language, what does H Gamma-1 mean?

A. H Gamma-1 is a type of vector of plasmid. Remember the plasmid loop or the DNA loop that I showed earlier, so it's a type of loop like that, and has a designation which is "P" for plasmid, "CD4" for CD4, and then "E" is the restriction enzyme -- I'm sorry, this is almost too technical -- but just to explain the terms, I think CD4 is obvious. The plasmid is obvious, and the other important part is the Gamma-1 which refers to IgG1.

Q. Okay. And is it correct that all of these structures were IgG1?

A. Yes. That's correct.
Q. Okay. So let's talk about the last structure, the Karjalainen structure. That's pCD4 H Gamma-1 of the '827 publication, which is JTX-60, and what type of structure is this one?
A. It's very similar to the one published by Seed, just uses a different restriction site, so, therefore, it's not E, but H.
Q. Okay. These were all CD4s. Right?
Was this concept of doing fusion proteins with receptors in human immunoglobulins, IgG1s, applied outside of the CD4 realm?
A. Yes, it was.
Q. Okay.
MS. RURKA: Let's take a look at the next demonstrative, which is DDX-1056.
BY MS. RURKA:
Q. And on here you have two constructs that have purple receptors. So, can you just generally tell us what you're showing here. What are these purple receptors?
A. Yeah. The reason I'm showing this, first of all, these constructs were made at the same time. But the reason I'm showing it is that they emphasize the concept that people understood, simulated and inspired by Dr. Capon's work, that you could use this type of a

construct to make different types of receptors that you could use to block other processes.

And so this is a particular example of a different receptor called a lymphocyte homing receptor shown in purple. That is meant to compete with a membrane-anchored or a cell-bound lymphocyte homing receptor. It's the same idea basically.

Q. What sort of treatment would a lymphocyte homing receptor fusion protein be directed to?

A. It was directed to treatment of inflammation, so that was spelled out in these publications.

Q. Okay. Thank you.

MS. RURKA: Let's go to JTX-61. We'll take a look -- I'm sorry.

If we could back up to the -- I want to just state for the record, we're talking about Watson 1990, which is at JTX-59, and Capon, the '964 patent of Dr. Capon, which is JTX-61.

And let's take a look at JTX-61.

BY MS. RURKA:

Q. And you reviewed this as part of your analysis, Doctor?

A. Yes, I did.

Q. And what is this?

A. This is a patent by Dr. Capon. It's a '964 patent,

and it was filed in November '89. Dr. Capon was at Genentech at the time.

Q. Okay. Let's turn to -- does Dr. Capon in this patent teach a preferred receptor?

A. Yes, he does.

Q. Which one?

A. It's the lymphocyte homing receptor.

Q. Okay.

MS. RURKA: Let's turn to Page 35 at Column 30, starting Line 42.

BY MS. RURKA:

Q. Okay. So what is Dr. Capon teaching is the use of these lymphocyte homing receptor IgG1 fusion proteins?

A. As I said earlier, the concept was to use this type of a receptor to compete for something. And in this case, the lymphocyte homing receptor immunoglobulin hybrid is employed therapeutically to compete with normal binding of lymphocytes.

So these are foreign inflammatory cells to lymphoid tissue. The hybrid is therefore particularly useful for organ or graft rejection or -- and this is important, I'm sorry -- and for treatment of patients with inflammation, such as are, for example, due to rheumatoid arthritis or other autoimmune diseases.

And an important point here is that Dr. Capon was

clearly proposing to use an Fc fusion protein to treat an inflammatory condition.

Q. Okay. Including rheumatoid arthritis?

A. Including rheumatoid arthritis, it says right there.

Q. Okay.

MS. RURKA: So let's go back to DDX-1057.

BY MS. RURKA:

Q. And can you just generally describe then what the evolution of the art was up until the point when the Roche applications were filed in August of 1990?

A. Yes, of course. So first thing, this was a very exciting field to make -- to use soluble receptors to block a function. And there was rapid evolution of a constructs and improvement starting with the breakthrough paper of Dr. Capon, that I've now mentioned a few times, who showed that you can actually make a CD4 immunoadhesin by coupling CD4 to an immunoglobulin.

Then rapidly thereafter, starting with the Traunecker paper that we just discussed, and that clearly taught to remove the CH1 domain, there were several other groups that made a very similar construct between different portions of CD4, mainly the entire extracellular domain and IgG1 coupling the fusion protein at the hinge, such that it includes the CH2 and CH3.

And essentially, the same concept was then applied to

a different type of receptor showing also that it was obvious to do so and attractive. And in this case, there are two examples of a different receptor, the lymphocyte homing receptor being attached to the hinge-CH2 and CH3 of an IgG1 to treat inflammatory conditions.

Q. Okay. Are you aware of real-world evidence showing that individuals other than the named inventors had actually used TNF receptors in these fusion proteins?

A. Yes, I am.

Q. Okay.

MS. RURKA: Let's take a look at DDX-1058. I think we have the wrong one. Okay. I apologize.

BY MS. RURKA:

Q. So, Doctor, what are we showing here on DDX-1058?

A. What I'm showing here is that four independent groups had the idea to fuse a TNF receptor to an IgG at the hinge.

Starting with Roche, that JTX-1 and JTX-2, those are the patents-in-suit, using the p55 TNF receptor that is in this case attached to the hinge of an immunoglobulin 3 or IgG3 molecule.

Then there was Immunex BehringWerke that took the p75 TNF receptor that was described by Immunex and Dr. Smith to generate p75 TNF receptor fusion protein with the hinge-CH2-CH3 domain of IgG1. This was later further developed into etanercept.

Genentech used the p55 extracellular domain of the TNF receptor linked again to a hinge-CH2 and CH3 of an IgG1.

And Dr. Bruce Beutler at UT Southwestern made a very similar construct where he also used the p55 TNF receptor extracellular domain attached to an IgG1.

And all had in mind to block the functions of TNF.

Q. Okay. And I think you said first we have Roche, and you weren't referring to who was first to come up with this structure?

A. No. I was just showing first on the left here on the slide.

Q. Okay. Thank you.

So let's talk specifically about Immunex's work, and you understand Immunex is not the inventors on the patents-in-suit here. Right?

A. I understand that.

Q. Okay. And Immunex worked with Behringwerke and you looked at some of their research. Isn't that right, Doctor?

MR. PRITIKIN: Your Honor, I have been loathe to object to leading questions, but I think the last one probably crossed the line.

THE COURT: You know what, go ahead and rephrase the question please.

MS. RURKA: Okay.

BY MS. RURKA:

Q. Did you look at any research related to the development of etanercept?

A. Yes, I did.

Q. What research did you look at?

A. I looked at evidence from Immunex and the collaboration between Immunex and the Behringwerke and Dr. Lauffer that describes the production of TNF -- p75 TNF receptors fused to IgG1.

Q. Okay. Can we please turn to DTX-111 in your binder.

And, Doctor, do you recognize this document?

A. Yes. This is a memorandum from Immunex from Dr. Dave Urdal to Steve Gillis, Mike Kranda and Pete Grassam. It refers to meeting notes from a meeting in October -- October 27, 1989, with Dr. Lauffer of the Behringwerke in Germany, who had visited Immunex on October 24th, 1989, to discuss receptors.

Q. And did you rely on this document in forming your opinion in this case?

A. Yes, I did.

Q. Okay. What was the subject matter of the meeting, Doctor?

A. The subject matter of the meeting was in fact Dr. Lauffer had been in Dr. Seed's lab for a while and was

also inspired by the use of TNFR fusion proteins. And so, they brought this idea to Immunex; why wouldn't we want to make a number of different fusion proteins with different receptors. And I have a demonstrative for that as well, or an evidence.

Q. Okay. So let's turn to the next page, and let's pull up the table.

And what sort of receptors were they looking at here, Doctor?

A. This is what the memorandum was referring to. And you can see here on the left side a number of different receptors. The names don't really matter. These are just interleukin receptors. These are pro-inflammatory receptors.

But the main thing is that this also lists a TNF receptor which had been cloned and, of course, this being a publication or memo coming from Immunex where Dr. Smith had just published the p75 TNF receptor sequence, that is clearly what is referred to here.

Q. Okay. And what sort of constructs were the meeting attendees discussing making with these receptors?

A. That is spelled out on the next paragraph here, if you could highlight that.

So this states that Dr. Lauffer had expected to obtain various cDNAs for receptors, including the TNF

receptor. And it also explains his motivation to do so. Let me find that sentence here. It starts here. Thank you.

So "We agreed that such a molecule may well be a drug with a longer half-life in vivo as well as one that could be readily purified by Protein A affinity techniques."

Q. And what such a molecule was he talking about?

A. He was talking about a fusion between the p75 TNF receptor to IgG1. And I know from studying this and the patent application by Dr. Seed that the construct they used and the preferred construct for them was IgG1 beginning at the hinge and then continuing through the CH2 and CH3 domain. So that was essentially etanercept.

Q. And do you know when that construct was made?

A. That construct was made, if I remember correctly, in July 1990, so, before the target date.

Q. Okay. So let's talk about the two motivating factors that are listed here. One is longer in vivo half-life and one is purified by Protein A affinity techniques. And can you discuss what those individual motivations are, just generally what they mean?

A. Yes. So, let me start by saying that, of course, the key motivation to make these types of receptor fusion proteins was that the receptor block the function of something. In case of the TNF receptor, of course it would

block the function of TNF.

But as I showed earlier, the receptors themselves were small, they were monomeric, and so, there was a need to improve their properties, and that's why these Fc fusion proteins were really such a brilliant idea.

Two of the key features that they impart on such a fusion protein are listed here, and I will talk about that some more, but one is that they improve the half-life of a fusion protein compared to the receptor on its own.

The receptors are small and are easily secreted into the urine. Making a fusion protein essentially makes them big enough that that does not happen. Patients don't like to be injected all the time, every few hours, with a drug. That's why.

And it's also important, if you think back to the purification of a molecule from cells, to have an easy way of doing that. And this particular technique, again without going into details, but Protein A affinity technique is a very easy way to purify a molecule. So those were key advantages.

Q. Okay. So let's turn to DTX-114 in your binder, briefly.

And have you seen this document before, Doctor?

A. Yes, I have. And this is what I was referring to as evidence that etanercept had been -- or the TNFR fusion

protein like etanercept had been produced by July 20, 1990.
Q. Okay. And did you rely on this in forming your opinions in this case?
A. Yes, I did.
Q. And what -- you say this has evidence of the production of the TNF receptor fusion protein -- and if you could turn to Paragraph 297. Sorry.
A. I believe it's up here. It says that -- it's Dr. Deeley.
Q. I'm sorry. What is Dr. Deeley reporting here?
A. Dr. Deeley, who was senior staff scientist, director of the department of gene expression at Immunex, is writing a letter to Dr. Lauffer to report that the Cos cells supernatants containing the human -- and this should be TNFR:Fc was tested there, so that means it was produced and sent there. And his interpretation of the data was that it was showing an amount of binding that he thought was actually worth pursuing. And I believe that's shown on the next paragraph.
Yes. In the first line it reads, In the meantime, I would conclude that your construct does indeed function as expected.
And so this tells me a number of things, including that the p75 TNF receptor Fc fusion protein like etanercept existed at the time and had been tested.

Q. Okay. Thank you.

MR. PRITIKIN: Your Honor, I'm going to object to these questions. They had a 102(g) defense that they dropped, and this is the sort of testimony that I think they were planning to proffer in support of it.

So I don't know why it's being offered, but to the extent that the witness is purporting to offer an opinion that there was a prior invention of etanercept, I think that's barred by the agreement and the limitations of the pretrial order.

THE COURT: Okay.

Ms. Rurka?

MS. RURKA: Yes, your Honor. They are well aware that we have been pursuing simultaneous invention. They have stated that Roche apparently was the first to have disclosed and invented this.

This is evidence of simultaneous invention. There's no surprise here. They know perfectly well that this was his opinion throughout this case.

THE COURT: Okay. And that's what you're seeking to elicit here is testimony regarding simultaneous invention?

MS. RURKA: Correct.

MR. PRITIKIN: Your Honor, as long as that's clear, that's fine. But we ought to be clear that this is not 102(g) testimony or a 102(g) defense.

THE COURT: So we'll get some final element of clarity in there. Ms. Rurka, Is that correct?

MS. RURKA: This is not 102(g) testimony, your Honor.

THE COURT: Thank you so much. Continue then.

MS. RURKA: Thank you.

BY MS. RURKA:

Q. Okay. So, we talked about the two motivations for Immunex, which is not the inventors-in-suit here, but the two motivations of plasma half-life and Protein A binding. So why don't we talk a little bit more about that and whether or not that was reported in the art at the time as motivations for making these fusion proteins.

What is half-life?

A. A half-life of a protein in this case refers to the half-life of it in the human body and, so, if you were to inject a drug into the bloodstream, it will circulate for a certain amount of time, and if it's below a certain cutoff, which has a size, it has a number, I'll say it's 60,000 daltons, the number doesn't matter so much, but if you're below that, and these receptors were about 30,000 dalton, you would have expected them to be rapidly lost and secreted in the urine. And in fact the inhibiters were purified from the urine, which further emphasizes that.

And it was well known that small molecules are simply

rapidly lost and, therefore, there was an incentive to make them larger and to keep them in the bloodstream longer precisely because patients don't like to inject themselves all the time, so this would give them a much longer interval between injections.

Q. Okay.

MS. RURKA: Let's go to DDX-1059.

BY MS. RURKA:

Q. And can you describe explain what the art was teaching with respect to plasma half-life with the fusion proteins?

A. Yes. What I put together here is some examples from the papers and reference that I cited earlier. First is Byrn 1990, JTX-56, at Page 1, which discusses the improved half-life characteristics of an Fc fusion protein with a receptor.

And Dr. Capon's '964 patent also states -- this is JTX-61 at Column 4, Line 38 to 43: It is an object of this invention to produce ligand-binding partners fused to moieties which serves to prolong the in vivo plasma half-life of ligand-binding partner such as immunoglobulin and domains.

Q. Okay. And so what are these teaching about use of fusion proteins to extend plasma half-life?

A. I mean, let me just say they teach the obvious. I'm

also a medical doctor, and I would have known that if you have a molecule that's small and secreted through the urine, it's rapidly lost. But they teach you a way to prevent that and to very dramatically improve the characteristics of these drugs compared to the receptors on their own.

Q. Okay. So let's talk about the second thing mentioned by Immunex and Behringwerke with respect to the construction of a molecule that is essentially the same as etanercept, Protein A affinity. What are Protein A affinity purification techniques?

A. Protein A affinity purification techniques use a protein that was found on a bacterium actually. It's called Protein A, and this bacterium uses it to turn antibodies around so it can't be attacked. It's sort of a trick. And scientists have used this protein for many, many years to purify various types of immunoglobulins.

The beauty of Protein A purification is that you can go from a pretty complex mixture, as you would find in the supernatant of a fermenter -- remember, that doesn't only contain the protein you told the cells to make but all of these other molecules that the cell is secreting and, so, you want to pull out your drug infusion protein, and Protein A is really a wonderful tool and a very well-established tool of doing so. By making Fc fusion

protein, you take advantage of that.

Q. Okay. And was that disclosed in the art?

A. It was.

MS. RURKA: Let's go to DDX-1060.

BY MS. RURKA:

Q. And can you just walk through what the disclosures are you have here on this slide?

A. It was abundantly disclosed. I've shown here four different examples from the publications we have discussed, and I think it emphasizes the point that everybody was aware of it.

This is Seed, the '262 patent, JTX-57 at Column 7, Line 22 to 24.

It reads, "IgG fusion proteins may be purified by passing a solution through a column which contains immobilized Protein A or Protein G" -- this is something very similar -- "which selectively binds the Fc portion of the fusion protein."

Dr. Capon's patent '964, JTX-61 at Column 4, Lines 38 to 43, states, "It is an object of this invention to produce ligand-binding partners fused to moieties which serve to prolong the in vivo half-life" -- we just discussed that -- "to facilitate its purification by Protein A."

Byrn 1990, JTX-56, at Page 2, Figure 1, says that you

can use these immunoadhesins or Fc fusion proteins, you can purify them to 99 percent of -- more than 99 percent purity using Protein A Sepharose chromatography as described.

And the Watson paper, JTX-59 at Page 4, also highlights, "Finally, the Protein A reactivity also allowed for the purification of this chimera to near homogeneity on Protein A Sepharose."

So let me just briefly emphasize the 99 percent purity, the near homogeneity, and the fact that everybody recognized this.

Q. Okay. Were there any, apart from longer plasma half-life and Protein A binding which would simplify purification, were there any other reasons why a person would be motivated to fuse the TNF receptor to an IgG1?

A. Yes. There was at least one more very important one, and that was to increase the avidity, if possible.

Q. Okay. Did any of the --

MS. RURKA: Can you turn to JTX-59? Sorry. JTX-59.

BY MS. RURKA::

Q. What is this document, Doctor?

A. This document is one of the documents we cited earlier. It describes the fusion protein between the homing receptor and the IgG Fc portion, and it's by Dr. Watson and colleagues at Genentech.

Q. And what does Dr. Watson teach about the avidity

effect?

A. Dr. Watson in the introduction teaches that this would be -- is in fact an attractive property of Fc fusion proteins because by making a dimer, you can increase the chances of having an increased avidity. And that's stated, I believe, on the next page.

MS. RURKA: Can we turn -- I think it's on Page 4. Can we turn to Page 4?

A. On Page 4, yes, at the --

MS. RURKA: Yes. Right at the top there.

A. So this spells it out, again something obvious, but this type of a molecule is the -- part of the -- missing part of the sentence, but it says it can dimerize, and that might be expected to add to the avidity of the interaction between the receptor and its ligand.

And that's an important property because if you have a soluble receptor and you're competing with receptors on the cell, you make it bind better. That's another advantage.

Q. Can you just generally give a little bit more detail about what "avidity" means and what -- why you would expect avidity to occur here?

A. Yes. So I'll try to explain that.

On the demonstrative I showed towards the beginning of TNF, which is a trimeric molecule, you would imagine

sort of a molecule with three different identical components, and now you have a receptor that can only bind to one of those components.

So it's like a hand that's trying to hold a ball that has three different parts, and it's actually quite easy to let go of that. But if at the same time you can use two hands to hold on to two parts of this trimeric TNF, you increase -- this is the avidity -- so the one hand would be an affinity; the two together is an avidity because, you know, the likelihood of them letting go is much, much lower.

And in scientific circles, for instance, as a POSA, you would say that that increases the effect of such a molecule by up to a thousandfold. So, it's actually a very important advantage. And you would get that in this case because TNF is a trimer. You would hope to get it.

Q. Okay. And you understand that one of the arguments that plaintiffs are making is that etanercept unexpectedly has improved binding. Right?

A. I understand that. But as a person of ordinary skill in the art and based on this very simple, essentially college-level concept, I would not consider this an unexpected property.

Q. Okay. And you said it's a college-level concept. Is it taught in any textbooks?

A. It's taught, for instance, in immunology textbooks.

MS. RURKA: Okay. Let's turn to DTX-84.

BY MS. RURKA:

Q. And what is this textbook, Doctor?

A. This is an immunology textbook by Dr. Ivan Roitt.

Q. And did you rely on this in forming your opinions in this case?

A. I didn't have to because I knew this, but it was a good example, actually, because it spells out this concept quite clearly.

Q. Okay.

MS. RURKA: So let's turn to Page 5, at Figure 7.7.

Q. And what does this --

MS. RURKA: Let's pull that up.

Q. And what does this figure teach about the expected binding properties of a dimer such as etanercept would be?

A. I'd really just like to go into the highlights here. And first of all is the title of this table. It's "Affinity and Avidity." And I'd really just like to focus on this construct here, these two IgG constructs.

Q. And just to orient the -- for the record, those are the middle two columns labeled "IgG" and "IgG?"

A. Exactly, those two columns. And without going into too much detail, let's just say here there's only one binding partner, and here there are two binding -- there

are two arms of an IgG and two binding partners that are linked.

And then if we look at the advantage of multivalence and simply highlight these two boxes, it says here what I also just stated earlier, that there is about a thousandfold advantage of having this.

And it also defines the terms whereas the --

MR. PRITIKIN: Your Honor, I'm going to object to this as outside the scope of the expert report.

THE COURT: Ms. Rurka.

MS. RURKA: Your Honor, it's right in his reply report, Paragraph 125.

THE COURT: Do you have a copy of that?

MS. RURKA: Yes, I do.

THE COURT: You know what, first if you could share with your adversary.

MS. RURKA: Sure.

MR. PRITIKIN: Your Honor, the expert report talks in general about avidity, and he gave that testimony earlier. But this chart that has been put up with the numbers comes from Paragraph 7.7, and all that's cited in the expert report is 7.3, which is sort of the general proposition.

So I think everything should be stricken that deals with Figure 7.7. The earlier testimony I think can stand. It's consistent with the report.

MS. RURKA: No, I'm sorry. Your Honor --

THE COURT: Yes.

MS. RURKA: -- it's actually Page 7.3. It's cited right here. This is Page 7.3.

Can you pull it out, please?

It's cited in Footnote 316 of his report: Roitt, I. M., et al., *Immunology*, 7.3. That's the page, not the figure.

THE COURT: Counsel, are you taking a look?

MR. PRITIKIN: Yeah. I think that is not the text that's pointed to here, and the chart is -- none of this is in the report.

MS. RURKA: Says in his report, A POSA would have been motivated to -- a POSA would have been motivated to design a TNF-binding protein to have an even higher affinity or avidity for TNF in order to compete for binding to its high-affinity native receptor.

And it cites the Smith patent.

Then it says, Avidity is a measure of the strength with which a multivalent antibody --

And then if you turn to -- I'm sorry. Can you pull up Roitt, please?

-- a multivalent antibody which --

Pull out that. That's the IgG. The second column that says IgG, that's a multivalent antigen.

It was known before August 1990 that when a multivalent antigen combines with more than one of an antibody's combining sites, the binding energy between the two is considerably greater than the sum of the binding energies of the individual sites since all the antigen antibody bonds must be broken simultaneously before the antigen and the antibody disassociate.

And he cites to this spot, this page, and also cites to, See also, *ibid.*, Multivalent binding between antibody and antigen, avidity or functional affinity, results in a considerable increase in stability as measured by the equilibrium constant compared to simple monovalent binding.

That's exactly what this chart is showing and what he's testifying to.

THE COURT: Counsel.

MR. PRITIKIN: It's a different section, your Honor. It's a different part that's been referenced.

THE COURT: Well, she says it's the same section, 7.3.

MS. RURKA: I literally just read from the legend, your Honor.

THE COURT: From the legend of Figure 7.7.

MS. RURKA: Which is on Page 7.3. It's not different. It's literally the same thing just talked about.

MR. PRITIKIN: The report has a footnote cite to the Immunology text.

THE COURT: Well, you know what, why don't we put it up on the screen.

MR. PRITIKIN: Sure.

THE COURT: Can you use the -- yeah. Pull it up, the ELMO or whatever device you have to pull it up.

MS. RURKA: Okay. Can you pull it up? Page 68. There you go. Put it on the screen. 317, I'm sorry, 316, 317.

THE COURT: Okay. Just show me where the exact citation is.

MS. RURKA: The citation is Roitt, 316. Roitt, I. M., et al., *Immunology*, 7.3. That's the page we were just looking at.

THE COURT: Okay.

MS. RURKA: And then the next cite is when I read that quote into the record, that's from the same page, from Figure 7.7, which we were just looking at.

THE COURT: Okay. What is the argument that it's not there? What do you read 7.3 to be? What is referenced here.

MR. PRITIKIN: First there is a threshold issue. This was not listed among the documents they were going to use to describe the state of the art, and that was the

objection that Mr. Heafner raised earlier.

Beyond that, if you actually look at the expert report, there is one sentence in it that says "Avidity is a measure of the strength with which a multivalent antibody binds to a multivalent antigen," and it's in quotation marks. And the cite then is to Footnote 316, which is to 7.3.

There is no mention of this Figure 7.7. None of those details are in the report. And there's not an indication in the report that they in any way intended to use that.

MS. RURKA: So, your Honor, the very next sentence says "It was known before August 1990," and it quotes specifically from that figure, and then it cites to it in Footnote 317.

THE COURT: When you're saying it cites to it specifically, that quote is from what document?

MS. RURKA: That quote is from Roitt, from the very spot we were looking at.

THE COURT: Okay. So, Mr. Pritikin, what is the issue? She's saying that quote is exactly from that.

MR. PRITIKIN: I don't think it is, your Honor. It's the numbers. It's talks the thousand-fold increase. If they had wanted him to testify about this, they have a long report. They could have described the table, they could

have talked about the numbers, the thousand-fold increase, whatever it is that's there. The quote they have comes from the bottom of the column --

THE COURT: Why don't we do it this way. What is Roitt Immunology 7.3?

MS. RURKA: That is the page we were just looking at. Can you put that back up. This is DTX-84 and and it's at 5, and this is Figure 7.7, this quote, Figure 7.7, Affinity and Avidity.

The very next sentence, Multivalent binding between antibody and antigen. Can you highlight that, please.

THE COURT: Well, actually just before we go to that, Figure 7.7 is distinct from the 7.3 that's referenced at the bottom.

MS. RURKA: 7.3 is the page that's on -- Figure 7.7 is on Page 7.3. Correct.

THE COURT: Okay. All right. You know what, now, hold that thought. Okay. What's the response to that?

MR. PRITIKIN: I think it helps to put up the whole page, your Honor, because we don't get the context here. All right. I think I can explain it.

THE COURT: Okay.

MR. PRITIKIN: Can I be heard about the -- I think I can explain it, your Honor.

THE COURT: Okay. Go ahead.

MR. PRITIKIN: All right. So, what the report does is to quote one sentence, and it has a footnote, and the footnote --

THE COURT: You know what, I'm going to go back to what I asked for initially. I said if someone has an extra copy, could you please hand that up? Thank you.

Let's see if we can bring this to a head. Go ahead.

MR. PRITIKIN: Let me see if I can explain this. So in the report we have the cite, the quote, the sentence that's quoted, and the sentence that's quoted comes from over here, the left column.

And then the longer quote that initially they talked about does not come from this box over here on the right. It actually is more text that's over here that follows on under Affinity and Avidity down here.

So everything that he quoted in the report came from down here, this lower left-hand column. The citation, all it does is tell you that where he got those quotes was from this page, 7.3. There is no mention of any of the numbers or the details or this box that appears in the right column.

And the reports are extensive in this case. If they had wanted Dr. Blobel to testify about these numbers, they certainly could have put it in the expert report. That's the basic problem.

Beyond that, this document is not one they identified as showing the state of the art.

So, where we come out, your Honor, is what I said a few minutes ago. The earlier testimony he gave in general as to what avidity and affinity are, that's fine. We don't have an objection to that.

But what we do have an objection to is introducing testimony relating to numbers and facts and boxes and things of this sort that had that detail in it that are not referenced in the expert report. And a casual reference to a page, particularly where you quoted text on it, is not sufficient to allow them to go into that with the expert here at trial.

MS. RURKA: So, your Honor, that's not an accurate characterization of the expert report.

So why don't we pull up -- can you pull up, please, the footnotes first. Let's pull up the footnotes. Okay.

There are two quotes here.

THE COURT: Right.

MS. RURKA: Not just the quote that's in the body.

THE COURT: Right.

MS. RURKA: There is also Footnote 317. And if you look at Footnote 317, it says, Multivalent binding between antibody and antigen (avidity or functional affinity) results in a considerable increase in stability as measured

by the equilibrium constant compared to simple monovalent binding.

That is a direct quote from Figure 7.7 which we just looked at. So if you back out and you look at Affinity and Avidity in DTX-84, starting at the -- so this Figure 7.7 is part of --

THE COURT: Yes.

MS. RURKA: -- the section, Affinity and Avidity, that he is saying was a different section. That is the same section. It's all one section and it's all about the very same concept which is --

THE COURT: Why don't you just highlight the section that you're saying is from 317 so we can all see it together.

MS. RURKA: Yes.

THE COURT: And I see it.

MS. RURKA: Figure 7.7, the statement right after Affinity and Avidity, that is the same quote that's in his expert report. If you go to the left-hand column, which is the beginning of this section -- I'm sorry -- the left-hand column, which is the beginning of this section, Affinity and Avidity, that's what this whole section is about.

And in here you have his statement also, When a multivalent antigen -- this is kind of six lines up.

When a multivalent antigen combines with more than

one of an antibody's combining sites, the binding energy between the two is considerably greater than the sum of the binding energies of the individual sites.

And that's what the chart is about that he was just talking about. It's just showing that when you, you have considerably greater avidity than the sum of the binding energies when you have more binding sites. That's all he was testifying to.

THE COURT: Okay. Anything further?

MR. PRITIKIN: Well, yes. I mean, this general proposition is fine. We don't quarrel with that. It's the details of the chart and the --

THE COURT: But it's in the same figure. Correct? Let me ask Ms. Rurka.

It's in the same figure? We just went through it. No?

MS. RURKA: It's the same figure we just looked at.

THE COURT: 7.7.

MS. RURKA: Correct.

THE COURT: All right. I'm going to let that go forward. You can do your cross on it. Go ahead.

MS. RURKA: Thank you.

BY MS. RURKA:

Q. Okay. So let's just orient the Court again. We were looking at Figure 7.7. There are two columns in the middle

of this table, IgG and IgG1.

Why don't you start with the left-hand column and describe what this left-hand IgG column is showing?

A. I really like to keep it simple. And basically, on the left-hand side you have an antibody with two arms just binding to -- let's say this was TNF, it would be binding to one sub-unit. It's drawn a little bit differently, but this would be a single binding interaction.

And here you would have an antibody that's simultaneously able to bind to two parts that are linked. I mean, that's basically the difference. Right? So if you have TNF trimer, you have one arm binding versus two that can bind to different parts. That's the concept here.

And then if we look at this particular part, the advantage of multivalence, it states that this is a ten-to-the-third advantage. That's a 1,000-fold advantage of having the multivalency. And it also defines the term.

On the left-hand side, the single interaction is called "affinity," and on the right-hand side the multiple interactions are called "avidity," which give you this advantage.

And so, surfing back to what we were discussing, this would have been an obvious advantage but also a desirable one from using a p75 TNF receptor coupled to a Fc fusion protein because TNF is a trimeric molecule so it has

multiple subunits, and you could hope to achieve this effect of avidity.

Q. Okay. And Doctor, what year is this textbook from?

A. Was it 1988?

Q. Let's go to DTX-84 at Page 2. And down at the bottom, bottom right, the copyright here on the bottom right.

A. Yes. So it was 1989.

Q. Okay. So why don't we just do a summary of -- actually why don't we just -- we'll talk a little bit about the hinge here briefly because the hinge is kind of an issue in the case. And you understand that plaintiffs -- that the construction of this hinge here is the exon-encoded hinge of an IgG1. Right?

A. Yes.

Q. Okay. And is it okay with you if I refer to that as a full hinge?

A. Yes.

Q. Okay. Would a person of skill in the art -- what would a person of skill in the art have thought about constructing a hinge for a TNF receptor IgG1 fusion protein?

A. The genetic definition would have been actually a very good way to go, simply because it contains three cysteines. So, you can essentially get three bonds that

hold the hinge in a way that would very clearly favor avidity. It wouldn't prove, you wouldn't know for sure that you would get an increased avidity. But if you wanted to try to achieve it, it would be better with a full hinge, the genomic definition of the hinge.

Q. Would other hinges be -- would a person skilled in the art be motivated to use other hinges?

A. You could also use other hinges, but this would be the preferred one.

Q. Okay. So let's walk through -- so now we've gone through most of your testimony and I just want to go through kind of the -- kind of painful exercise of discussing where in the art -- what combinations and where in the art those combinations can be found. Okay.

So let's go to DDX-1062, and these are the six combinations that we were required to make to narrow down our case in this case. So what are those six combinations?

A. The first combination is Smith '760 patent in view of Seed '262 publication.

The second is Smith '760 patent in view of the Byrn 1990 publication.

The third is Smith '760 patent in view of Watson 1990.

The fourth is Smith '760 patent in view of Karjalainen '827 publication.

The fifth is Smith '760 patent in view of Capon '964 patent and Traunecker 1989 paper.

And the six is Smith 1990 in view of Watson 1990.

Q. Okay. And let's go to DTX-1064. And what is this chart? What is the DDX-1064? I apologize. And what is this chart showing here, Doctor?

A. This chart shows the exact page numbers where these references can be looked up.

Q. Okay. So let's walk through this as quickly as we can. And what is on the left-hand column here, Doctor?

A. On the left-hand column I showed the different parts that we talked about for the '182 and the '522 patents.

First of all, the p75 TNF receptor part and TNF binding. The blue part is the receptor IgG fusion protein, for example, fused at the hinge-CH2-CH3. And the third is the culturing in a host cell, for example, CHO cells, and to purify the protein.

And so I spelled out the exact lines and portions of the references that I consulted that contain text pertinent to these issues.

Q. Okay. Let's talk first about the p75 TNF receptor and TNF binding. And where is that disclosed in the art specifically?

A. In the Smith '760 patent, which is JTX-65, it's in Column 2, Line 67 to Column 3, Line 6. It can also be

found in Column 3, Line 16 to 26; Column 9, Line 16 to 29; Column 10, Lines 53 to 68; Column 16, Lines 60 to 66; and in Figures 2A and 2B.

With respect to the culture of a host cell --

Q. I'm sorry. We're still on the p75 TNF receptor and TNF binding.

A. Yes.

Q. Where else is that disclosed in the art?

A. It's also disclosed in the Smith publication, which is JTX-24, on Page 1, Page 3 and Page 4.

Q. Okay. And where is the receptor IgG fusion protein, the hinge-CH2-CH3 or portions of the IgG disclosed in the art?

A. In the Seed '262 publication, that's JTX-57, Column 10, Line 56; third Column 11, Line 2, in Table 2; and in Column 57, Line 1, through Column 58, Line 55.

Q. And for Byrn 1990?

A. Byrn 1990 is JTX-56. That's a paper so the relevant information is on Page 1, on Page 2, on Page 3 to 4, and in Figure 1.

Q. Okay. And for the Watson 1990 JTX-59, where can you find this information?

A. On Page 1, Page 2, and in Figure 1A.

Q. For the Karjalainen '827 publication, which is JTX-60, where can you find this information?

A. It's Column 6, Line 44 to Column 7, Line 35. And the Figure 2, which shows the plasmid I described earlier, the pCD4-H Gamma 1.

Q. And for the Capon '964 patent, JTX-61, where can you find these elements?

A. Column 1, Line 8 to 14; Column 4, Line 16 to 43; Column 7, Line 13 to 19; Column 15, Line 4 to 18, Example 4.

Q. And where can you find the elements in the Traunecker 1999 paper, JTX-25?

A. On Page 1, 2 and 3, Figure 1.

Q. Okay. And then the last element, which is the claims -- for the claims of the '522 patent, is culturing host cell, including CHO cells and purifying proteins.

And where can you find that -- where can you find discussions or disclosures of those steps in the art?

A. In the Smith patent, the '760 patent, that's JTX-65, Column 14, Line 5 to 15; Column 15, Line 60 to Column 16, Line 56.

Q. How about the Seed '262 publication, JTX-57?

A. Column 6, Line 23 to 24; Column 6, Line 28 to 32; Column 7, Line 20 to 26; Column 57, Line 16 to Column 58, Line 55.

Q. And how about the Byrn 1990 publication at JTX-56?

A. Page 2, Figure 1.

Q. How about Watson 1990 at JTX-59?
A. Page 2 and Page 4.
Q. In the Capon '964 patent, JTX-61?
A. Column 16, Line 10 to 11; Column 29, Line 30 to 48; Column 30, Line 26 to 37; Column 40, Line 68 to Column 41, Line 2; and Column 44, Line 67 to Column 45, Line 9.
Q. Okay. And finally, for the Traunecker 1989 paper, JTX-25, where would you find the element of culturing host cells and purifying proteins?
A. In Figure 2.
Q. Okay. What would be the expected activity of this fusion protein with a p75 TNF receptor in an IgG1 hinge-CH2 and CH3?
A. The expected activity would be that it binds TNF.
Q. And would that have been expected in 1990?
A. Yes.
Q. Okay. You understand that Dr. Wall has opined that a person of skill in the art would have been discouraged from fusing TNF receptors to immunoglobulins due to what he says are effector functions. You understand that. Right?
A. I understand that.
Q. And what are effector functions?
A. Effector functions are functions that can be elicited by antibodies, such as complement-dependent cell lysis or CDC and, what is it, antibody-dependent cell, ADCC -- I

actually forget what does that stand for -- antibody, yeah.

Anyway, ADCC is one of the effector functions where killer cells bind to antibodies and will kill the target cell.

Q. Do you agree with Dr. Wall this would have discouraged the development of -- the attachment of TNF receptors to immunoglobulins?

A. Absolutely not.

Q. Let's turn to DDX-1066. And what do you have prepared here, Doctor?

A. I prepared a table or a chart providing examples of references at the time that would not have taught away from the claimed invention for those reasons.

Q. Okay. And why don't we walk through them one at a time. Number 1 is Smith '760 patent, teaches construction of p75 TNF receptor IgG1 -- why don't you explain Number 1 to us?

A. Yeah. Number 1 is the Smith '760 patent that we've actually discussed at quite some length today, which teaches construction of a p75 TNF receptor IgG1 fusion protein, and it was meant to block the functions of TNF in the context of inflammation, so that certainly does not raise that as an issue.

Then there was real-world simultaneous invention of TNF receptor IgG fusion proteins show that scientists were

not discouraged. And that was the meeting in October 1989 by Immunex -- between Immunex and the Behringwerke that I discussed, and the July 1990 letter from Immunex to Behringwerke.

And in addition, in 1991 -- that's JTX-69 -- a group from Genentech, led by Dr. Eshkenazi, also described TNF receptor IgG fusion protein, as did Dr. Peppel, who was in Bruce Beutler's group, and that paper was published in 1991. That's JTX-68. All of them meant to block the functions of TNF and they were not concerned about possible effector functions.

Then the third point is prior art development of anti-TNF antibodies.

Antibodies are, of course, true immunoglobulins that contain acetomines * and they would, by definition, have all effector functions.

There was no concern, in any of the several manuscripts I consulted looking at the production of TNF antibodies to block TNF.

Here's some examples: Brennan 1989, DTX-75; Hinshaw 1990, DTX-79; and Piguet, 1987, DTX-82.

And in addition, in an example that I actually did discuss, the prior art teaches receptor IgG fusion proteins for treating inflammatory conditions, including rheumatoid arthritis, which is a quote that I read from the -- that's

from the Watson paper, I believe, or the Capon patent.

Q. And that's JTX-59 for the Watson paper and JTX-61 for the Capon patent?

A. That's correct.

Q. Okay. We're almost done.

So, you understand Claims 35 and 36 of the '182 patent recite a plasmid that was deposited in October of 2006. Correct?

A. Yes.

Q. Okay. Assuming that those claims would only be entitled to a 2006 priority date, would the claims be obvious?

A. They would be obvious, and, of course, etanercept was on the market at the time. It was -- it came on the market in 1999.

Q. Okay. Finally, let's talk about the last double patenting opinion. We should be able to get through this quickly. It's the Brockhaus '279 patent.

Let's turn to JTX-5 in your binder.

And can you identify this document?

A. Yes. This is the Brockhaus '279 patent, filed by Dr. Brockhaus at Hoffmann-La Roche.

Q. So are these the same inventors as on the patents-in-suit?

A. Yes.

Q. Okay. Let's turn to Claim 5, which is the last -- second-to-last page, Claims 1 through 5.

And you understand that that Claim 5 eventually, kind of multiply depends all the way back to Claim 1. Do you understand that?

A. That's correct.

MS. RURKA: And let's pull up DDX-1069, so we can get kind of an easier look at what Claim 5 claims.

Q. So can you walk through Claim 5 of the '279 patent and what it relates to.

A. Yes, I can. And again, this is color-coded. So in sort of pink, I'm showing a soluble fragment of the insoluble TNF receptor protein, wherein said insoluble TNF receptor protein has an molecular weight of about 55 kilodaltons, as determined by SDS-polyacrylamide gel. That is shown in pink here and corresponds to the p55 TNF receptor extracellular domain.

And the second subsequence, so the fusion protein encodes all of the domains of the constant region of the human immunoglobulin heavy chain other than the first domain of said constant region. And so we've discussed this at length in the context of the '182 and '522 patents. That's the hinge-CH2-CH3.

Q. And what is -- which IgG is specified in Claim 5?

A. Claim 5 says that this is IgG1.

Q. Okay. Did you perform a comparison of the Claim 5 with all the elements of Claim 1 to the claims -- the asserted claims in the patents, the '182 patent?

A. Yes, I did.

Q. Okay.

MS. RURKA: Let's pull that up.

Q. And can you inform the Court what the actual differences are?

A. So, the differences are -- so they're very similar. The main difference is actually the use of a different receptor. It's the p75 TNF receptor in the '182 patent, and the p55 receptor in the '279 patent. And the --

Q. Is that a meaningful difference?

A. It's not a meaningful difference because both receptors can inhibit TNF, so you would have been motivated to replace the p55 with the p75.

Q. And then the last element inherently, specifically, where it said proteins specifically binds human TNF, is that found in the claims of the '279 patent?

A. It is in that. It's also stated inherently and specifically binds human TNF.

Q. Okay. I have no further questions. Thank you.

THE COURT: All right. Thank you so much.

Let's discuss our schedule because right now it looks like it's 4:46. What would you propose?

MR. PRITIKIN: Your Honor, what I would propose is perhaps we should adjourn for the day and pick up with the cross first thing in the morning.

THE COURT: I believe that's fine. How long do you anticipate on cross?

MR. PRITIKIN: It's hard to know for sure. I know, having overnight, I can try to streamline it a little bit.

THE COURT: Okay. I'm not holding you to anything. I'm just trying to get an idea.

MR. PRITIKIN: Ballpark, maybe three or four hours.

THE COURT: Okay. And then we'll do a little bit -- I guess there's going to be a little bit more from the defendants with this witness, and then we're going to have our next witness lined up.

MR. LOMBARDI: Dr. McCamish.

THE COURT: And if he is not able to be completed tomorrow, then when do you propose bringing him back?

MR. LOMBARDI: We really need to get him in tomorrow.

THE COURT: Did he not have two days? Didn't he have the 14th as well?

MR. LOMBARDI: I think you're right, your Honor. I think you're right about that.

THE COURT: We're going to try, but I'm just trying to determine what was the other date. I know there was one in one of the letters sent in.

MR. LOMBARDI: 14th is Friday, I think.

THE COURT: I think so. Let me just check.

14th is Friday.

MR. LOMBARDI: And if we said that before, it's correct and I've just forgotten.

THE COURT: Not a problem.

MR. LOMBARDI: That will work.

THE COURT: We'll do our best.

What else do we have in terms of scheduling for tomorrow? Anything in terms of a wrinkle?

MR. LOMBARDI: If we need to fill in time; if, for instance, something happens and Dr. McCamish doesn't get on or whatever, we do have depositions that we will be playing for your Honor.

THE COURT: That sounds good. Fair enough. But it sounds like tomorrow is going to be fully occupied and dealt with because we have cross with this witness and then we have the next witness lined up. So I guess tomorrow should be okay.

Anything else that you can envision?

MR. ABRAHAM: Judge, I had a question of procedure.

THE COURT: Yes.

MR. ABRAHAM: Now that we concluded the direct examination of this witness, ordinarily we think we'd be able to work and prepare for cross-examination. We just

want to make sure that our rules align with what the Court's rule is and that it fully governs, obviously, for the trial.

THE COURT: Obviously. Have you spoken about that at all? Have you folks spoken?

MS. WALSH: We have not, your Honor.

THE COURT: Do you want to take a moment and talk to one another about this?

I'm going to excuse the witness from the stand at this point, and I'm going to instruct you as to your communications with counsel in a moment.

(Witness excused.)

THE COURT: You know what, if counsel want to just come forward for a moment.

(Sidebar conference held off the record.)

THE COURT: I was just speaking with counsel off the record about the procedure that we would employ with respect to conversations with witnesses, whether it's direct, whether it's cross.

We have concluded ultimately that there are going to be no conversations with the witnesses at any point in time once they start their testimony, and that applies to both sides, to the plaintiff and the defendants. And I think everyone understands that and is in agreement with that.

Is that not correct, counsel?

MR. PRITIKIN: Fine with us, your Honor.

MR. ABRAHAM: Yes, your Honor.

THE COURT: And with respect to exhibits, I propose the following: Since we are in the middle of this witness, perhaps it might be productive if you take this evening to compare your lists on the exhibits, have those in order so we can enter them in the morning.

And I indicated that it would be a good idea to do them each day, but it's at the end of the day now, we're in the middle of the witness, and I'd rather have them accurate. So take sometime to compare the list with one another and I'll be ready to put them on the record tomorrow.

How does that sound?

MS. RURKA: That's acceptable, your Honor.

MR. PRITIKIN: That's fine with us.

THE COURT: Anything else before we conclude?

MR. PRITIKIN: Nothing from us, your Honor.

MS. RURKA: Nothing, your Honor.

THE COURT: Thank you so much. I look forward to seeing you tomorrow. Take care, everyone.

(The proceedings are concluded at 4:55 p.m.)

* * *